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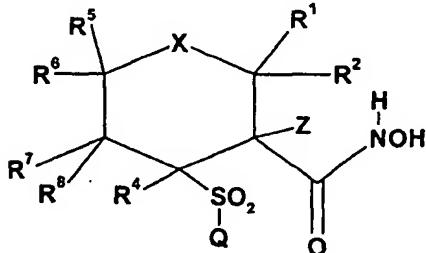
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(54) Gem substituted sulfonyl hydroxamic acids as MMP inhibitors

(57) A compound of the formula



wherein R¹-R¹³, X, Z and Q are as defined above, useful in the treatment of arthritis, cancer, and other diseases involving the dysregulated production/release of reproxlyns such as Aggrecanase and other diseases characterized by matrix metalloproteinase activity. In addition, the compounds of the present invention may be used in combination therapy with standard non-steroidal anti-inflammatory drugs (NSAID's), COX-2 inhibitors and analgesics, and in combination with cytotoxic drugs such as adriamycin, daunomycin, cis-platinum, etoposide, taxol, taxotere and other alkaloids, such as vincristine, in the treatment of cancer.

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DescriptionBackground of the Invention

5 [0001] The present invention relates to geminal disubstituted cyclic hydroxamic acids and derivatives thereof, and to pharmaceutical compositions comprising such derivatives and to the use of such derivatives in the treatment of arthritis, cancer and other diseases. The present invention also relates to treating arthritis in a mammal, comprising administering to such mammal an effective amount of an inhibitor with potent or differential MMP or reproxysin activity (preferably wherein said inhibitor is selective for Aggrecanase over MMP-1, or MMP-13 and/or Aggrecanase over MMP-1).

10 [0002] The compounds of the present invention are inhibitors of zinc metalloendopeptidases, especially those belonging to the matrix metalloproteinase (also called MMP or matrixin) and reproxysin (also known as adamylsin) subfamilies of the metzincins (Rawlings, *et al.*, Methods in Enzymology, 248, 183-228 (1995) and Stocker, *et al.*, Protein Science, 4, 823-840 (1995)).

15 [0003] The MMP subfamily of enzymes currently contains seventeen members (MMP-1, MMP-2, MMP-3, MMP-7, MMP-8, MMP-9, MMP-10, MMP-11, MMP-12, MMP-13, MMP-14, MMP-15, MMP-16, MMP-17, MMP-18, MMP-19, MMP-20). The MMP's are most well known for their role in regulating the turn-over of extracellular matrix proteins and as such play important roles in normal physiological processes such as reproduction, development and differentiation. In addition, the MMP's are expressed in many pathological situations in which abnormal connective tissue turnover is occurring. For example, MMP-13 an enzyme with potent activity at degrading type II collagen (the principal collagen in cartilage), has been demonstrated to be overexpressed in osteoarthritic cartilage (Mitchell, *et al.*, J. Clin. Invest., 97, 761 (1996)). Other MMPs (MMP-2, MMP-3, MMP-8, MMP-9, MMP-12) are also overexpressed in osteoarthritic cartilage and inhibition of some or all of these MMP's is expected to slow or block the accelerated loss of cartilage typical of joint diseases such as osteoarthritis or rheumatoid arthritis.

20 [0004] The mammalian reproxysins are known as ADAMs (A Disintegrin And Metalloproteinase) (Wolffberg, *et al.*, J. Cell Biol., 131, 275-278 (1995)) and contain a disintegrin domain in addition to a metalloproteinase-like domain. To date twenty-three distinct ADAM's have been identified.

25 [0005] ADAM-17, also known as tumor necrosis factor-alpha converting enzyme (TACE), is the most well known ADAM. ADAM-17 (TACE) is responsible for cleavage of cell bound tumor necrosis factor-alpha (TNF- α , also known as cachectin). TNF- α is recognized to be involved in many infectious and autoimmune diseases (W. Fiers, FEBS Letters, 285, 199 (1991)). Furthermore, it has been shown that TNF- α is the prime mediator of the inflammatory response seen in sepsis and septic shock (Spooner, *et al.*, Clinical Immunology and Immunopathology, 62 S11 (1992)). There are two forms of TNF- α , a type II membrane protein of relative molecular mass 26,000 (26 kD) and a soluble 17 kD form generated from the cell bound protein by specific proteolytic cleavage. The soluble 17 kD form of TNF- α is released by the cell and is associated with the deleterious effects of TNF- α . This form of TNF- α is also capable of acting at sites distant from the site of synthesis. Thus, inhibitors of TACE prevent the formation of soluble TNF- α and prevent the deleterious effects of the soluble factor (see United States Patent 5,830,742 issued November 3, 1998).

30 [0006] Select compounds of the invention are potent inhibitors of Aggrecanase, an enzyme important in the degradation of cartilage aggrecan. Aggrecanase is also believed to be an ADAM. The loss of aggrecan from the cartilage matrix is an important factor in the progression of joint diseases such as osteoarthritis and rheumatoid arthritis and inhibition of Aggrecanase is expected to slow or block the loss of cartilage in these diseases.

35 [0007] Other ADAMs that have shown expression in pathological situations include ADAM TS-1 (Kuno, *et al.*, J. Biol. Chem., 272, 556-562 (1997)), and ADAM's 10, 12 and 15 (Wu, *et al.*, Biochem. Biophys. Res. Comm., 235, 437-442, (1997)). As knowledge of the expression, physiological substrates and disease association of the ADAM's increases the full significance of the role of inhibition of this class of enzymes will be appreciated.

40 [0008] The compounds of the present invention are useful in the treatment of diseases in which inhibition of MMP's and/or ADAM's will provide therapeutic benefit, such as those characterized by matrix metalloproteinase or ADAM expression.

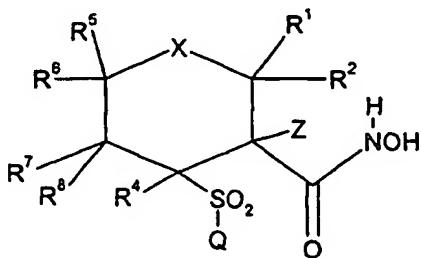
45 [0009] The present inventor has also discovered that it is possible to identify inhibitors with differential metalloprotease and reproxysin activity (preferably MMP-13 or Aggrecanase inhibitory activity). One group of preferred inhibitors include those molecules which selectively inhibit Aggrecanase and matrix metalloprotease-13 (MMP-13) preferentially over MMP-1. Another group of preferred inhibitors include those molecules which selectively inhibit Aggrecanase preferentially over MMP-1. Another group of preferred inhibitors include those molecules which selectively inhibit MMP-13 preferentially over MMP-1.

50 [0010] Matrix metalloproteinase and reproxysin inhibitors are well known in the literature. Specifically, European Patent Publication 606,046, published July 13, 1994 refers to certain heterocyclic MMP inhibitors. PCT Publication WO 98/08825 and WO 98/08815, both published March 5, 1998, refer to certain cyclic hydroxamic acid MMP inhibitors. United States Patent 5,861,510, issued January 19, 1999, refers to cyclic arylsulfonylamino hydroxamic acids that are

useful as MMP inhibitors. PCT Publication WO 98/34918, published August 13, 1998, refers to cyclic hydroxamic acids including certain dialkyl substituted compounds that are useful as MMP inhibitors. PCT publications WO 96/27583 and WO 98/07697, published March 7, 1996 and February 26, 1998, respectively, refer to arylsulfonyl hydroxamic acids. PCT publication WO 98/03516, published January 29, 1998, refers to phosphinates with MMP activity. PCT publication 5 98/33768, published August 6, 1998, refers to N-unsubstituted arylsulfonylamino hydroxamic acids. European Patent Publication EP 935,963, published August 18, 1999 refers to the use of MMP-13 selective inhibitors for the treatment of osteoarthritis. European Patent Publications 949,245; 949,246 and 952,148, published October 13, 1999, October 10 13, 1999 and October 27, 1999, respectively, refer to methods of preparing hydroxamic acids. United States Provisional Patent Application 60/148464 entitled "Selective Inhibitors of Aggrecanase in Osteoarthritis Treatment," filed August 12, 1999 refers to MMP, Aggrecanase and TACE inhibitors and to additional methods of preparing hydroxamic acids. PCT Publications WO 00/09485 and WO 00/09492, both published February 24, 2000, refer to heterocyclic hydroxamic acids. PCT Publication WO 99/05291, published February 4, 1999, refers to Aggrecanase. Each of the above referenced publications and applications is hereby incorporated by reference in its entirety.

15 Summary of the Invention

[0011] The present invention relates to a compound of the formula



or the pharmaceutically acceptable salts thereof, wherein

35 X is oxygen, sulfur, >SO, >SO₂ or >NR³;
 Z is -OR¹¹, -NR¹²R¹³ or (C₁-C₆)alkyl optionally substituted with one to three substituents (preferably zero, one or two substituents, most preferably zero or one substituent) independently selected from the group consisting of halo, hydroxy, -CN, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₆-C₁₀)aryl(C₂-C₆)alkenyl, (C₁-C₉)heteroaryl(C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₆-C₁₀)aryl(C₂-C₆)alkynyl, (C₁-C₉)heteroaryl(C₂-C₆)alkynyl, amino, (C₁-C₆)alkylamino, [(C₁-C₆)alkyl]₂amino, mercapto, (C₁-C₆)alkylthio, (C₁-C₆)alkoxy, perfluoro(C₁-C₆)alkyl, perfluoro(C₁-C₆)alkoxy, (C₆-C₁₀)aryl, (C₁-C₉)heteroaryl, (C₃-C₉)heterocyclic, (C₃-C₉)cycloalkyl, (C₆-C₁₀)aryl amino, (C₆-C₁₀)arylthio, (C₅-C₁₀)aryloxy, (C₁-C₉)heteroaryl amino, (C₁-C₉)heteroarylthio, (C₁-C₉)heteroaryl oxy, (C₃-C₉)heterocyclic-amino, (C₃-C₉)heterocyclic-S-, (C₃-C₉)heterocyclic-O-, (C₃-C₉)cycloalkylamino, (C₃-C₉)cycloalkyl-S-, (C₃-C₉)cycloalkyl-O-, (C₁-C₆)alkyl-(C=O)-, (C₁-C₆)alkyl-(C=O)-NH-, (C₁-C₆)alkyl-(C=O)-S-, (C₁-C₆)alkyl-(C=O)-O-, (C₁-C₆)alkoxy-(C=O)-, -CO₂H, H₂N-(C=O)-, (C₁-C₆)alkyl-NH-(C=O)- and [(C₁-C₆)alkyl]₂-N-(C=O)-;

40 R¹, R², R⁵ and R⁶ are each independently selected from the group consisting of hydrogen, -CN, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₆-C₁₀)aryl(C₂-C₆)alkenyl, (C₁-C₉)heteroaryl(C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₆-C₁₀)aryl(C₂-C₆)alkynyl, (C₁-C₉)heteroaryl(C₂-C₆)alkynyl, perfluoro(C₁-C₆)alkyl, (C₆-C₁₀)aryl, (C₁-C₉)heteroaryl, (C₃-C₉)cycloalkyl, (C₃-C₉)heterocyclic, (C₁-C₆)alkyl(C=O)-, (C₁-C₆)alkoxy-(C=O)-, -CO₂H, H₂N-(C=O)-, (C₁-C₆)alkyl-NH-(C=O)- and [(C₁-C₆)alkyl]₂-N-(C=O)-;

45 wherein said R¹, R², R⁵ and R⁶ (C₁-C₆)alkyl groups are each independently optionally substituted by one to three groups (preferably one or two groups, more preferably one group) selected from halo, trifluoromethyl, hydroxy, amino, -CN, (C₁-C₆)alkylthio, (C₁-C₆)alkoxy, (C₆-C₁₀)aryl, (C₁-C₉)heteroaryl, (C₃-C₆)cycloalkyl, (C₃-C₉)heterocyclic, (C₆-C₁₀)aryl amino, (C₆-C₁₀)arylthio, (C₆-C₁₀)aryloxy, (C₁-C₉)heteroaryl amino, (C₁-C₉)heteroarylthio, (C₁-C₉)heteroaryl oxy, (C₃-C₉)heterocyclic-amino, (C₃-C₉)heterocyclic-S-, (C₃-C₉)heterocyclic-O-, (C₃-C₉)cycloalkylamino, (C₃-C₉)cycloalkyl-S-, (C₃-C₉)cycloalkyl-O-, (C₆-C₁₀)aryl(C₁-C₂)alkoxy, (C₁-C₉)heteroaryl(C₁-C₂)alkoxy, (C₁-C₆)alkyl-(C=O)-NH-, (C₁-C₆)alkyl-(C=O)-S-, (C₁-C₆)alkyl-(C=O)-O-, (C₁-C₆)alkylsulfinyl, (C₆-C₁₀)aryl sulfinyl, (C₁-C₆)alkylsulfonyl, (C₆-C₁₀)aryl sulfonyl, (C₁-C₆)alkylamino, or ((C₁-C₆)alkyl)₂amino;

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R³ is hydrogen; (C₁-C₆)alkyl optionally substituted by one or more of -CN, perfluoro(C₁-C₆)alkyl, (C₆-C₁₀)aryl, (C₃-C₆)cycloalkyl, (C₁-C₆)alkyl(C=O)-, (C₁-C₆)alkoxy-(C=O)-, -CO₂H, (C₁-C₆)alkyl-NH-(C=O)-, and [(C₁-C₆)alkyl]₂N-(C=O)-; (C₆-C₁₀)arylsulfonyl; (C₁-C₆)alkylsulfonyl; (C₁-C₆)alkyl-NH-(C=O)-; [(C₁-C₆)alkyl]₂N-(C=O)-; or (R¹⁰R⁹N)-(C=O)- wherein R⁹ and R¹⁰ are taken together with the nitrogen to which they are attached to form a ring selected from azetidinyl, pyrrolidinyl, piperidinyl, morpholinyl and thiomorpholinyl; (more preferably R³ is hydrogen or (C₁-C₃)alkyl);

R⁴ is hydrogen or (C₁-C₄)alkyl;

R^7 and R^8 are each independently selected from the group consisting of hydrogen, hydroxy, halo, -CN, (C_1 - C_6)alkyl, (C_2 - C_6)alkenyl, (C_2 - C_6)alkynyl, amino, (C_1 - C_6)alkylamino, $[(C_1$ - C_6)alkyl] $_2$ amino, (C_1 - C_6)alkylthio, (C_1 - C_6)alkoxy, perfluoro(C_1 - C_6)alkyl, perfluoro(C_1 - C_6)alkoxy, (C_3 - C_6)cycloalkyl, (C_6 - C_{10})aryl, (C_3 - C_9)heterocyclic, (C_1 - C_9)heteroaryl, (C_6 - C_{10})arylamino, (C_6 - C_{10})arylthio, (C_6 - C_{10})aryloxy, (C_1 - C_9)heteroarylthio, (C_1 - C_9)heteroarylxy, (C_3 - C_9)heterocyclic-amino, (C_3 - C_9)heterocyclic-S-, (C_3 - C_9)heterocyclic-O-, (C_3 - C_9)cycloalkylamino, (C_3 - C_9)cycloalkyl-S-, (C_3 - C_9)cycloalkyl-O-, (C_6 - C_{10})aryl(C_2 - C_6)alkenyl, (C_1 - C_9)heteroaryl(C_2 - C_6)alkenyl, (C_6 - C_{10})aryl(C_2 - C_6)alkynyl, (C_1 - C_9)heteroaryl(C_2 - C_6)alkynyl, (C_1 - C_6)alkyl(C=O)-, (C_1 - C_6)alkyl(C=O)-NH-, (C_1 - C_6)alkyl(C=O)-S-, (C_1 - C_6)alkyl(C=O)-O-, (C_1 - C_6)alkoxy-(C=O)-, -CO₂H, H₂N-(C=O)-, (C_1 - C_6)alkyl-NH-(C=O)- and $[(C_1$ - C_6)alkyl] $_2$ -N-(C=O)-;

wherein each of said R⁷ and R⁸ (C₁-C₆)alkyl groups are independently optionally substituted by one to three substituents (preferably one to two substituents, more preferably one substituent) independently selected from halo, hydroxy, -CN, (C₁-C₆)alkoxy, (C₁-C₆)alkylthio, trifluoromethyl, (C₃-C₆)cycloalkyl, (C₆-C₁₀)aryl, (C₃-C₉)heterocyclic, (C₁-C₉)heteroaryl, (C₆-C₁₀)arylamino, (C₆-C₁₀)arylthio, (C₆-C₁₀)aryloxy, (C₁-C₉)heteroaryl amino, (C₁-C₉)heteroarylthio, (C₁-C₉)heteroarylxy, (C₃-C₉)heterocyclic-amino, (C₃-C₉)heterocyclic-S-, (C₃-C₉)heterocyclic-O-, (C₃-C₉)cycloalkylamino, (C₃-C₉)cycloalkyl-S-, (C₃-C₉)cycloalkyl-O-, (C₆-C₁₀)aryl(C₁-C₂)alkoxy, (C₁-C₉)heteroaryl(C₁-C₂)alkoxy, (C₁-C₆)alkyl(C=O)-NH-, (C₁-C₆)alkyl(C=O)-S-, (C₁-C₆)alkyl(C=O)-O-, (C₁-C₆)alkylsulfinyl, (C₆-C₁₀)aryl sulfinyl, (C₁-C₆)alkylsulfonyl, (C₆-C₁₀)arylsulfonyl, amino, (C₁-C₆)alkylamino and ((C₁-C₆)alkyl)₂amino;

or R¹ and R², R⁵ and R⁶ or R⁷ and R⁸ may be taken together to form a carbonyl group or an optionally substituted (C₃-C₆)cycloalkyl ring optionally containing 1 or 2 heteroatoms; wherein said heteroatoms may be selected from the group consisting of -S-, -O- or >NH or >N(C₁-C₆)alkyl; and said optional substituents (i.e. 1-3 substituents per ring) may be selected from (C₁-C₄)alkyl, fluoro, chloro, hydroxy, (C₁-C₄)alkoxy and -NR¹⁴R¹⁵;

or R⁵ and R⁷, R⁵ and R⁸, R⁶ and R⁷ or R⁶ and R⁸ may be taken together to form an optionally substituted (C₄-C₆) cycloalkyl ring optionally containing 1 or 2 heteroatoms; wherein said heteroatoms may be selected from the group consisting of -S-, -O- or >NH or >N(C₁-C₆)alkyl; and said optional substituents (i.e. 1-3 substituents) may be selected from (C₁-C₄)alkyl, fluoro, chloro, hydroxy, (C₁-C₄)alkoxy and -NR¹⁴R¹⁵;

R¹¹ is hydrogen, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₆-C₁₀)aryl(C₂-C₆)alkenyl, (C₂-C₉)heteroaryl(C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₆-C₁₀)aryl(C₂-C₆)alkynyl, (C₁-C₉)heteroaryl(C₂-C₆)alkynyl, perfluoro(C₁-C₆)alkyl, (C₆-C₁₀)aryl, (C₁-C₉)heteroaryl, (C₃-C₆)cycloalkyl, (C₃-C₉)heterocyclic, (C₁-C₆)alkyl-(C=O)-, (C₁-C₆)alkoxy-(C=O)-, (C₁-C₆)alkyl-NH-(C=O)- or [(C₁-C₆)alkyl]₂-N-(C=O)-;

R₁₂ is hydrogen, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₆-C₁₀)aryl(C₂-C₆)alkenyl, (C₁-C₉)heteroaryl(C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₆-C₁₀)aryl(C₂-C₆)alkynyl, (C₁-C₉)heteroaryl(C₂-C₆)alkynyl, perfluoro(C₁-C₆)alkyl, (C₆-C₁₀)aryl, (C₁-C₉)heteroaryl, (C₃-C₆)cycloalkyl, (C₃-C₉)heterocyclic, (C₁-C₆)alkyl-(C=O)-, (C₁-C₆)alkoxy-(C=O)-, H₂N-(C=O)-, (C₁-C₆)alkyl-NH-(C=O)- or [(C₁-C₆)alkyl]₂-N-(C=O)-;

R¹³ is hydrogen, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₆-C₁₀)aryl(C₂-C₆)alkenyl, (C₁-C₉)heteroaryl(C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₆-C₁₀)aryl(C₂-C₆)alkynyl, (C₁-C₉)heteroaryl(C₂-C₆)alkynyl, perfluoro(C₁-C₆)alkyl, (C₆-C₁₀)aryl, (C₁-C₉)heteroaryl, (C₁-C₆)cycloalkyl or (C₁-C₉)heterocyclic;

R^{14} is hydrogen, (C_1-C_6) alkyl, (C_2-C_6) alkenyl, (C_6-C_{10}) aryl (C_2-C_6) alkenyl, (C_1-C_9) heteroaryl (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, (C_6-C_{10}) aryl (C_2-C_6) alkynyl, (C_1-C_9) heteroaryl (C_2-C_6) alkynyl, perfluoro (C_1-C_6) alkyl, (C_6-C_{10}) aryl, (C_1-C_9) heteroaryl, (C_3-C_6) cycloalkyl, (C_3-C_9) heterocyclic, (C_1-C_6) alkyl- $(C=O)$ -, (C_1-C_6) alkoxy- $(C=O)$ -, $H_2N-(C=O)$ -, (C_1-C_6) alkyl- $NH-(C=O)$ - or $[(C_1-C_6)$ alkyl] $_2$ - $N-(C=O)$ -;

R^{15} is hydrogen, (C_1-C_6) alkyl, (C_2-C_6) alkenyl, (C_6-C_{10}) aryl (C_2-C_6) alkenyl, (C_1-C_9) heteroaryl (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, (C_6-C_{10}) aryl (C_2-C_6) alkynyl, (C_1-C_9) heteroaryl (C_2-C_6) alkynyl, perfluoro (C_1-C_6) alkyl, (C_6-C_{10}) aryl, (C_1-C_9) heteroaryl, (C_3-C_6) cycloalkyl or (C_3-C_9) heterocyclic;
 Q is (C_1-C_6) alkyl, (C_6-C_{10}) aryl, (C_1-C_9) heteroaryl, (C_3-C_9) heterocyclic, (C_6-C_{10}) aryl (C_1-C_6) alkyl, (C_1-C_9) heteroar-

yl(C₁-C₆)alkyl, (C₃-C₉)heterocyclic(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₆-C₁₀)aryl, (C₆-C₁₀)aryl(C₁-C₉)heteroaryl, (C₆-C₁₀)aryl(C₃-C₉)heterocyclic, (C₁-C₉)heteroaryl(C₆-C₁₀)aryl, (C₁-C₉)heteroaryl(C₁-C₉)heteroaryl, (C₁-C₉)heteroaryl(C₃-C₉)heterocyclic, (C₃-C₉)heterocyclic(C₆-C₁₀)aryl, (C₃-C₉)heterocyclic(C₁-C₉)heteroaryl, (C₃-C₉)heterocyclic(C₃-C₉)heterocyclic, (C₆-C₁₀)aryloxy(C₁-C₆)alkyl, (C₆-C₁₀)aryloxy(C₆-C₁₀)aryl, (C₆-C₁₀)aryloxy(C₁-C₉)heteroaryl,

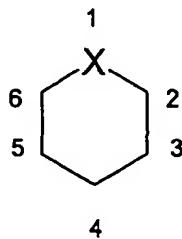
(C₆-C₁₀)aryloxy(C₃-C₉)heterocyclic, (C₁-C₉)heteroaryloxy(C₁-C₆)alkyl, (C₁-C₉)heteroaryloxy(C₆-C₁₀)aryl, (C₁-C₉)heteroaryloxy(C₁-C₉)heteroaryl, (C₁-C₉)heteroaryloxy(C₃-C₉)heterocyclic, (C₃-C₉)heterocyclic-O-(C₁-C₆)alkyl, (C₃-C₉)heterocyclic-O-(C₆-C₁₀)aryl, (C₃-C₉)heterocyclic-O-(C₁-C₉)heteroaryl, (C₃-C₉)heterocyclic-O-(C₃-C₉)het-

erocyclic, (C₆-C₁₀)aryl(C₁-C₆)alkyl(C₆-C₁₀)aryl, (C₆-C₁₀)aryl(C₁-C₆)alkyl(C₁-C₉)heteroaryl, (C₆-C₁₀)aryl(C₁-C₆)alkyl(C₃-C₉)heterocyclic, (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C₆-C₁₀)aryl, (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C₁-C₉)heteroaryl, (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C₃-C₉)heterocyclic, (C₆-C₁₀)aryloxy(C₁-C₆)alkyl(C₆-C₁₀)aryl, (C₆-C₁₀)aryloxy(C₁-C₆)alkyl(C₁-C₉)heteroaryl, (C₆-C₁₀)aryloxy(C₁-C₆)alkyl(C₃-C₉)heterocyclic, (C₁-C₉)heteroaryl(C₁-C₆)alkyl(C₆-C₁₀)aryl, (C₁-C₉)heteroaryl(C₁-C₆)alkyl(C₁-C₉)heteroaryl, (C₁-C₉)heteroaryl(C₁-C₆)alkoxy(C₆-C₁₀)aryl, (C₁-C₉)heteroaryl(C₁-C₆)alkoxy(C₁-C₉)heteroaryl, (C₁-C₉)heteroaryl(C₁-C₆)alkoxy(C₃-C₉)heterocyclic, (C₁-C₉)heteroaryloxy(C₁-C₆)alkyl(C₆-C₁₀)aryl, (C₁-C₉)heteroaryloxy(C₁-C₆)alkyl(C₁-C₉)heteroaryl, (C₁-C₉)heteroaryloxy(C₁-C₆)alkyl(C₃-C₉)heterocyclic, (C₃-C₉)heterocyclic(C₁-C₆)alkyl(C₆-C₁₀)aryl, (C₃-C₉)heterocyclic(C₁-C₆)alkyl(C₁-C₉)heteroaryl, (C₃-C₉)heterocyclic(C₁-C₆)alkyl(C₃-C₉)heterocyclic, (C₃-C₉)heterocyclic(C₁-C₆)alkoxy(C₆-C₁₀)aryl, (C₃-C₉)heterocyclic(C₁-C₆)alkoxy(C₁-C₉)heteroaryl, (C₃-C₉)heterocyclic(C₁-C₆)alkoxy(C₃-C₉)heterocyclic, (C₃-C₉)heterocyclic-O-(C₁-C₆)alkyl(C₆-C₁₀)aryl, (C₃-C₉)heterocyclic-O-(C₁-C₆)alkyl(C₁-C₉)heteroaryl, (C₃-C₉)heterocyclic-O-(C₁-C₆)alkyl(C₃-C₉)heterocyclic, (C₆-C₁₀)aryl(C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₆-C₁₀)aryl-NH-(C₁-C₆)alkyl, (C₆-C₁₀)aryl-NH-(C₆-C₁₀)aryl, (C₆-C₁₀)aryl-NH-(C₁-C₉)heteroaryl, (C₆-C₁₀)aryl-NH-(C₃-C₉)heterocyclic, (C₁-C₉)heteroaryl-NH-(C₁-C₆)alkyl, (C₁-C₉)heteroaryl-NH-(C₆-C₁₀)aryl, (C₁-C₉)heteroaryl-NH-(C₁-C₉)heteroaryl, (C₁-C₉)heteroaryl-NH-(C₃-C₉)heterocyclic, (C₃-C₉)heterocyclic-NH-(C₁-C₆)alkyl, (C₃-C₉)heterocyclic-NH-(C₆-C₁₀)aryl, (C₃-C₉)heterocyclic-NH-(C₁-C₉)heteroaryl, (C₃-C₉)heterocyclic-NH-(C₃-C₉)heterocyclic, (C₆-C₁₀)aryl(C₁-C₆)alkyl-NH-(C₆-C₁₀)aryl, (C₆-C₁₀)aryl(C₁-C₆)alkyl-NH-(C₁-C₉)heteroaryl, (C₆-C₁₀)aryl(C₁-C₆)alkyl-NH-(C₃-C₉)heterocyclic, (C₆-C₁₀)aryl(C₁-C₆)alkyl(C₆-C₁₀)aryl, (C₆-C₁₀)aryl-NH-(C₁-C₆)alkyl(C₁-C₉)heteroaryl, (C₆-C₁₀)aryl-NH-(C₃-C₉)heterocyclic, (C₁-C₉)heteroaryl(C₁-C₆)alkyl-NH-(C₆-C₁₀)aryl, (C₁-C₉)heteroaryl(C₁-C₆)alkyl-NH-(C₃-C₉)heterocyclic, (C₁-C₉)heteroaryl(C₁-C₆)alkyl-NH-(C₁-C₉)heteroaryl, (C₁-C₉)heteroaryl(C₁-C₆)alkyl-NH-(C₃-C₉)heterocyclic, (C₁-C₉)heteroaryl(C₁-C₆)alkyl-NH-(C₆-C₁₀)aryl, (C₁-C₉)heteroaryl(C₁-C₆)alkyl-NH-(C₁-C₉)alkyl or (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C₁-C₆)alkyl, wherein each of said (C₆-C₁₀)aryl, (C₁-C₉)heteroaryl or (C₃-C₉)heterocyclic groups (wherever they occur) may optionally be substituted by one or more substituents, preferably one to three substituents per ring, most preferably one to three substituents on the terminal ring independently selected from the group consisting of halo, -CN, (C₁-C₆)alkyl optionally substituted with one or more fluorine atoms, hydroxy, hydroxy-(C₁-C₆)alkyl, (C₁-C₆)alkoxy optionally substituted with one or more fluorine atoms, (C₁-C₆)alkoxy(C₁-C₆)alkyl, HO-(C=O)-, (C₁-C₆)alkyl-O-(C=O)-, HO-(C=O)-(C₁-C₆)alkyl, (C₁-C₆)alkyl-O-(C=O)-(C₁-C₆)alkyl, (C₁-C₆)alkyl-(C=O)-O-, (C₁-C₆)alkyl-(C=O)-O-(C₁-C₆)alkyl, H(O=C)-, H(O=C)-(C₁-C₆)alkyl, (C₁-C₆)alkyl(O=C)-, (C₁-C₆)alkyl, NO₂, amino, (C₁-C₆)alkylamino, [(C₁-C₆)alkyl]₂amino, amino(C₁-C₆)alkyl, (C₁-C₆)alkylamino(C₁-C₆)alkyl, [(C₁-C₆)alkyl]₂amino(C₁-C₆)alkyl, H₂N-(C=O)-, (C₁-C₆)alkyl-NH-(C=O)-, [(C₁-C₆)alkyl]₂N-(C=O)-(C₁-C₆)alkyl, H(O=C)-NH-, (C₁-C₆)alkyl(C=O)-NH, (C₁-C₆)alkyl(C=O)-[NH](C₁-C₆)alkyl, (C₁-C₆)alkyl(C=O)-[N(C₁-C₆)alkyl](C₁-C₆)alkyl, (C₁-C₆)alkyl-S-, (C₁-C₆)alkyl-(S=O)-, (C₁-C₆)alkyl-SO₂-²⁻, (C₁-C₆)alkyl-SO₂-NH-, (C₁-C₆)alkyl-SO₂-[N-(C₁-C₆)alkyl]-, H₂N-SO₂-²⁻, H₂N-SO₂-(C₁-C₆)alkyl, (C₁-C₆)alkylHN-SO₂-(C₁-C₆)alkyl, [(C₁-C₆)alkyl]₂N-SO₂-(C₁-C₆)alkyl, CF₃SO₂-²⁻, (C₁-C₆)alkyl-SO₂-²⁻, phenyl, phenyl(C₁-C₆)alkyl, (C₃-C₁₀)cycloalkyl, (C₁-C₉)heterocycloalkyl, and (C₁-C₉)heteroaryl.

40 [0012] The term "D- or L-amino acid", as used herein, unless otherwise indicated, includes glycine, alanine, valine, leucine, isoleucine, phenylalanine, asparagine, glutamine, tryptophan, proline, serine, threonine, tyrosine, hydroxyproline, cysteine, cystine, methionine, aspartic acid, glutamic acid, lysine, arginine or histidine.

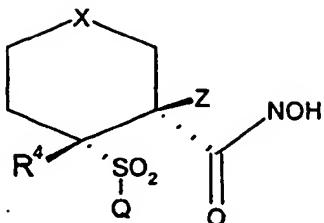
45 [0013] The positions on the ring of formula I, as used herein, are defined as follows:

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[0014] The compound of formula I may have chiral centers and therefore exist in different enantiomeric forms. This invention relates to all optical isomers, diasteriomers, atropisomers, stereoisomers and tautomers of the compounds of formula I and mixtures thereof. The preferred stereochemistry is as follows:



15 [0015] The present invention also relates to the pharmaceutically acceptable acid addition salts of compounds of the formula I. The acids which are used to prepare the pharmaceutically acceptable acid addition salts of the aforementioned base compounds of this invention are those which form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, such as the hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, acetate, lactate, citrate, acid citrate, tartrate, bitartrate, succinate, maleate, fumarate, glutamate, saccharate, benzoate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate and pamoate [i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)]salts.

20 [0016] The invention also relates to base addition salts of formula I. The chemical bases that may be used as reagents to prepare pharmaceutically acceptable base salts of those compounds of formula I that are acidic in nature are those that form non-toxic base salts with such compounds. Such non-toxic base salts include, but are not limited to those derived from such pharmacologically acceptable cations such as alkali metal cations (e.g., potassium and sodium) and alkaline earth metal cations (e.g., calcium and magnesium), ammonium or watersoluble amine addition salts such as N-methylglucamine-(meglumine), and the lower alkanolammonium and other base salts of pharmaceutically acceptable organic amines.

25 [0017] The subject invention also includes isotopically-labelled compounds, which are identical to those recited in Formula I, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as ^2H , ^3H , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F , and ^{36}Cl , respectively. Compounds of the present invention, prodrugs thereof, and pharmaceutically acceptable salts of said compounds or of said prodrugs which contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this invention. Certain isotopically-labelled compounds of the present invention, for example those into which radioactive isotopes such as ^3H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., ^3H , and carbon-14, i.e., ^{14}C , isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium, i.e., ^2H , can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. Isotopically-labelled compounds of Formula I of this invention and prodrugs thereof can generally be prepared by carrying out the procedures disclosed in the Schemes and/or in the Examples and Preparations below, by substituting a readily available isotopically-labelled reagent for a non-isotopically-labelled reagent.

30 [0018] As used herein, the term "alkyl," as well as the alkyl moieties of other groups referred to herein (e.g., alkoxy), may be linear or branched (such as methyl, ethyl, n-propyl, isopropyl, n-butyl, iso-butyl, *secondary*-butyl, *tertiary*-butyl), and they may also be cyclic (e.g., cyclopropyl or cyclobutyl); optionally substituted by 1 to 3 suitable substituents as defined below such as fluoro, chloro, trifluoromethyl, $(\text{C}_1\text{-C}_6)$ alkoxy, $(\text{C}_6\text{-C}_{10})$ aryloxy, trifluoromethoxy, difluoromethoxy or $(\text{C}_1\text{-C}_6)$ alkyl. The phrase "each of said alkyl" as used herein refers to any of the preceding alkyl moieties within a group such alkoxy, alkenyl or alkylamino. Preferred alkyls include $(\text{C}_1\text{-C}_4)$ alkyl, most preferably methyl.

35 [0019] As used herein, the term "cycloalkyl" refers to a mono or bicyclic carbocyclic ring (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclopentenyl, cyclohexenyl, bicyclo[2.2.1]heptanyl, bicyclo[3.2.2]octanyl and bicyclo[5.2.0]nonanyl, etc.); optionally containing 1-2 double bonds and optionally substituted by 1 to 3 suitable substituents as defined below such as fluoro, chloro, trifluoromethyl, $(\text{C}_1\text{-C}_6)$ alkoxy, $(\text{C}_6\text{-C}_{10})$ aryloxy, trifluoromethoxy, difluoromethoxy or $(\text{C}_1\text{-C}_6)$ alkyl, more preferably fluoro, chloro, methyl, ethyl and methoxy.

40 [0020] As used herein, the term "halogen" includes fluoro, chloro, bromo or iodo or fluoride, chloride, bromide or iodide.

45 [0021] As used herein, the term "mercapto" refers to the group -SH.

50 [0022] As used herein, the term "halo-substituted alkyl" refers to an alkyl radical as described above substituted with

one or more halogens included, but not limited to, chloromethyl, dichloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, 2,2,2-trichloroethyl, and the like; optionally substituted by 1 to 3 suitable substituents as defined below such as fluoro, chloro, trifluoromethyl, (C₁-C₆)alkoxy, (C₆-C₁₀)aryloxy, trifluoromethoxy, difluoromethoxy or (C₁-C₆)alkyl.

[0023] As used herein, the term "alkenyl" means straight or branched chain unsaturated radicals of 2 to 6 carbon atoms, including, but not limited to ethenyl, 1-propenyl, 2-propenyl (allyl), *iso*-propenyl, 2-methyl-1-propenyl, 1-but enyl, 2-but enyl, and the like; optionally substituted by 1 to 3 suitable substituents as defined below such as fluoro, chloro, trifluoromethyl, (C₁-C₆)alkoxy, (C₆-C₁₀)aryloxy, trifluoromethoxy, difluoromethoxy or (C₁-C₆)alkyl.

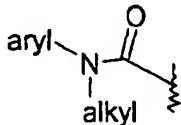
[0024] As used herein, the term "(C₂-C₆)alkynyl" is used herein to mean straight or branched hydrocarbon chain radicals having one triple bond including, but not limited to, ethynyl, propynyl, butynyl, and the like; optionally substituted by 1 to 3 suitable substituents as defined below such as fluoro, chloro, trifluoromethyl, (C₁-C₆)alkoxy, (C₆-C₁₀)aryloxy, trifluoromethoxy, difluoromethoxy or (C₁-C₆)alkyl.

[0025] As used herein, the term "alkoxyiminy" refers to a group of the formula -C=N-O-R, wherein R is alkyl or aryl optionally substituted with a suitable substituent. Examples of such groups are methoxyiminy and phenoxyiminy.

[0026] As used herein, the term "carbonyl" (as used in phrases such as alkylcarbonyl or alkoxy carbonyl) refers to the joinder of the >C=O moiety to a second moiety such as an alkyl or amino group (i.e. an amido group). Alkoxy carbonyl amino (i.e. alkoxy(C=O)-NH-) refers to an alkyl carbamate group. The carbonyl group is also equivalently defined herein as (C=O). Alkylcarbonyl amino refers to groups such as acetamide.

[0027] As used herein, the term "(C₁-C₆)alkyl-[(C₆-C₁₀)aryl-]N-(C=O)" as used herein, refers to a disubstituted amide group of the formula

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[0028] As used herein, the term "aryl" means aromatic radicals such as phenyl, naphthyl, tetrahydronaphthyl, indanyl and the like; optionally substituted by 1 to 3 suitable substituents as defined below such as fluoro, chloro, trifluoromethyl, (C₁-C₆)alkoxy, (C₆-C₁₀)aryloxy, trifluoromethoxy, difluoromethoxy or (C₁-C₆)alkyl, more preferably fluoro, chloro, methyl, ethyl and methoxy.

[0029] As used herein, the term "heteroaryl" refers to an aromatic heterocyclic group usually with one heteroatom selected from O, S and N in the ring. In addition to said heteroatom, the aromatic group may optionally have up to four N atoms in the ring. For example, heteroaryl group includes pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, thienyl, furyl, imidazolyl, pyrrolyl, oxazolyl (e.g., 1,3-oxazolyl, 1,2-oxazolyl), thiazolyl (e.g., 1,2-thiazolyl, 1,3-thiazolyl), pyrazolyl, tetrazolyl, triazolyl (e.g., 1,2,3-triazolyl, 1,2,4-triazolyl), oxadiazolyl (e.g., 1,2,3-oxadiazolyl), thiadiazolyl (e.g., 1,3,4-thiadiazolyl), tetrazole, quinolyl, isoquinolyl, benzothienyl, benzofuryl, indolyl, and the like; optionally substituted by 1 to 3 suitable substituents as defined below such as fluoro, chloro, trifluoromethyl, (C₁-C₆)alkoxy, (C₆-C₁₀)aryloxy, trifluoromethoxy, difluoromethoxy or (C₁-C₆)alkyl, more preferably fluoro, chloro, methyl, ethyl and methoxy. Particularly preferred heteroaryl groups include pyridyl, pyrimidinyl, pyrazinyl, quinolyl, isoquinolyl, thienyl and thiazolyl (these heteroaryls are the more preferred of the Q heteroaryls, more preferably the terminal Q heteroaryl moiety, most preferably optionally substituted pyridin-3-yl, pyridin-4-yl, quinolin-3-yl, quinolin-4-yl, quinolin-5-yl, quinolin-6-yl, isoquinolin-3-yl, isoquinolin-4-yl, isoquinolin-5-yl, isoquinolin-6-yl, pyrazinyl and pyrimidin-5-yl).

[0030] The term "heterocyclic" as used herein refers to a cyclic group containing 3-9 carbon atoms and 1-4 heteroatoms selected from N, O, S or NR'. Examples of monocyclic saturated or partially saturated ring systems are tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, imidazolidin-1-yl, imidazolidin-2-yl, imidazolidin-4-yl, pyrrolidin-1-yl, pyrrolidin-2-yl, pyrrolidin-3-yl, piperidin-1-yl, piperidin-2-yl, piperidin-3-yl, piperazin-1-yl, piperazin-2-yl, piperazin-3-yl, 1,3-oxazolidin-3-yl, isothiazolidine, 1,3-thiazolidin-3-yl, 1,2-pyrazolidin-2-yl, 1,3-pyrazolidin-1-yl, thiomorpholine, 1,2-tetrahydrothiazin-2-yl, 1,3-tetrahydrothiazin-3-yl, tetrahydrothiadiazine, morpholine, 1,2-tetrahydrodiazin-2-yl, 1,3-tetrahydrodiazin-1-yl, 1,4-oxazin-2-yl, 1,2,5-oxathiazin-4-yl and the like; optionally substituted by 1 to 3 suitable substituents as defined below such as fluoro, chloro, trifluoromethyl, (C₁-C₆)alkoxy, (C₆-C₁₀)aryloxy, trifluoromethoxy, difluoromethoxy or (C₁-C₆)alkyl, more preferably fluoro, chloro, methyl, ethyl and methoxy.

[0031] As used herein, the term "a suitable substituent" is intended to mean a chemically and pharmaceutically acceptable functional group i.e., a moiety that does not negate the inhibitory activity of the inventive compounds. Such suitable substituents may be routinely selected by those skilled in the art. Illustrative examples of suitable substituents include, but are not limited to halo groups, perfluoroalkyl groups, perfluoroalkoxy groups, alkyl groups, hydroxy groups, oxo groups, mercapto groups, alkylthio groups, alkoxy groups, aryl or heteroaryl groups, aryloxy or heteroaryloxy groups, aralkyl or heteroaralkyl groups, aralkoxy or heteroaralkoxy groups, -CO₂H groups, amino groups, alkyl- and

dialkylamino groups, carbamoyl groups, alkylcarbonyl groups, alkoxy carbonyl groups, alkylaminocarbonyl groups dialkylamino carbonyl groups, arylcarbonyl groups, aryloxycarbonyl groups, alkylsulfonyl groups, and arylsulfonyl groups and the like.

[0032] An embodiment of the present invention includes compounds of formula I, referred to as the Tetrahydropyran Group of compounds are those compounds wherein X is -O-. Another embodiment of the present invention includes compounds of formula I, referred to as the Tetrahydrothiopyran Group of compounds are those compounds wherein X is -S-. Another embodiment of the present invention includes compounds of formula I, referred to as the Tetrahydrothiopyran oxide Group of compounds are those compounds wherein X is >S=O. Another embodiment of the present invention includes compounds of formula I, referred to as the Tetrahydrothiopyran-1,1-dioxide Group of compounds are those compounds wherein X is >SO₂. Another embodiment of the present invention includes compounds of formula I, referred to as the Piperidine Group of compounds are those compounds wherein X is >NR³.

[0033] An embodiment of the present invention includes compounds of formula I, referred to as the hydroxy-Tetrahydropyran Group of compounds are those compounds wherein X is -O- and Z is -OR¹¹ and R¹¹ is hydrogen. Another embodiment of the present invention includes compounds of formula I, referred to as the hydroxy-Tetrahydrothiopyran Group of compounds are those compounds wherein X is -S- and Z is -OR¹¹ and R¹¹ is hydrogen. Another embodiment of the present invention includes compounds of formula I, referred to as the hydroxy-Tetrahydrothiopyran oxide Group of compounds are those compounds wherein X is >S=O and Z is -OR¹¹ and R¹¹ is hydrogen. Another embodiment of the present invention includes compounds of formula I, referred to as the hydroxy-Tetrahydrothiopyran-1,1-dioxide Group of compounds are those compounds wherein X is >SO₂ and Z is -OR¹¹ and R¹¹ is hydrogen. Another embodiment of the present invention includes compounds of formula I, referred to as the hydroxy-Piperidine Group of compounds are those compounds wherein X is >NR³ and Z is -OR¹¹ and R¹¹ is hydrogen.

[0034] An embodiment of the present invention includes compounds of formula I, referred to as the Tetrahydropyran-Ether Group of compounds are those compounds wherein X is -O- and Z is -OR¹¹ and R¹¹ is other than hydrogen. Another embodiment of the present invention includes compounds of formula I, referred to as the Tetrahydrothiopyran-Ether Group of compounds are those compounds wherein X is -S- and Z is -OR¹¹ and R¹¹ is other than hydrogen. Another embodiment of the present invention includes compounds of formula I, referred to as the Tetrahydrothiopyran-1,1-dioxide-Ether Group of compounds are those compounds wherein X is >SO₂ and Z is -OR¹¹ and R¹¹ is other than hydrogen. Another embodiment of the present invention includes compounds of formula I, referred to as the Piperidine-Ether Group of compounds are those compounds wherein X is >NR³ and Z is -OR¹¹ and R¹¹ is other than hydrogen.

[0035] An embodiment of the present invention includes compounds of formula I, referred to as the Amino-Tetrahydropyran Group of compounds are those compounds wherein X is -O- and Z is -NR¹²R¹³. Another embodiment of the present invention includes compounds of formula I, referred to as the Amino-Tetrahydrothiopyran Group of compounds are those compounds wherein X is -S- and Z is -NR¹²R¹³. Another embodiment of the present invention includes compounds of formula I, referred to as the Amino-Tetrahydrothiopyran oxide Group of compounds are those compounds wherein X is >S=O and Z is -NR¹²R¹³. Another embodiment of the present invention includes compounds of formula I, referred to as the Amino-Tetrahydrothiopyran-1,1-dioxide Group of compounds are those compounds wherein X is >SO₂ and Z is -NR¹²R¹³. Another embodiment of the present invention includes compounds of formula I, referred to as the Amino-Piperidine Group of compounds are those compounds wherein X is >NR³ and Z is -NR¹²R¹³.

[0036] An embodiment of the present invention includes compounds of formula I, referred to as the Alkyl-Tetrahydropyran Group of compounds are those compounds wherein X is -O- and Z is (C₁-C₆)alkyl. Another embodiment of the present invention includes compounds of formula I, referred to as the Alkyl-Tetrahydrothiopyran Group of compounds are those compounds wherein X is -S- and Z is (C₁-C₆)alkyl. Another embodiment of the present invention includes compounds of formula I, referred to as the Alkyl-Tetrahydrothiopyran oxide Group of compounds are those compounds wherein X is >S=O and Z is (C₁-C₆)alkyl. Another embodiment of the present invention includes compounds of formula I, referred to as the Alkyl-Tetrahydrothiopyran-1,1-dioxide-Ether Group of compounds are those compounds wherein X is >SO₂ and Z is (C₁-C₆)alkyl. Another embodiment of the present invention includes compounds of formula I, referred to as the Alkyl-Piperidine Group of compounds are those compounds wherein X is >NR³ and Z is (C₁-C₆)alkyl.

[0037] Preferred compounds of the present invention are those wherein X is >NR³, more preferably wherein R³ is hydrogen.

[0038] Other preferred compounds of the present invention are those wherein X is -O-.

[0039] Most preferred compounds of the present invention are those wherein Z is -OR¹¹, more preferably wherein R¹¹ is hydrogen, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, perfluoro(C₁-C₆)alkyl, (C₆-C₁₀)aryl, (C₁-C₉)heteroaryl, (C₃-C₆)cycloalkyl, (C₃-C₉)heterocyclic, (C₁-C₆)alkyl-(C=O)-, (C₁-C₆)alkoxy-(C=O)- or (C₁-C₆)alkyl-NH-(C=O)-; more preferably hydrogen, (C₁-C₄)alkyl or (C₂-C₄)alkenyl; most preferably wherein R¹¹ is hydrogen.

[0040] Other preferred compounds of the present invention are those wherein Z is -NR¹²R¹³, more preferably wherein

R¹² is hydrogen, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₆-C₁₀)aryl, (C₁-C₉)heteroaryl, (C₃-C₆)cycloalkyl, (C₃-C₉)heterocyclic, (C₁-C₆)alkyl-(C=O)-, (C₁-C₆)alkoxy-(C=O)-, H₂N-(C=O)-, (C₁-C₆)alkyl-NH-(C=O)-, or [(C₁-C₆)alkyl]₂-N-(C=O)-; more preferably wherein R¹² is hydrogen, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₆-C₁₀)aryl; more preferably wherein R¹² is hydrogen, (C₁-C₆)alkyl or (C₂-C₆)alkenyl; and wherein R¹³ is hydrogen, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₆-C₁₀)aryl, (C₁-C₉)heteroaryl, (C₃-C₆)cycloalkyl or (C₃-C₉)heterocyclic; more preferably wherein R¹³ is hydrogen, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl or (C₆-C₁₀)aryl; more preferably wherein R¹³ is hydrogen, (C₁-C₆)alkyl or (C₂-C₆)alkenyl; most preferably wherein R¹³ is hydrogen. Most preferred compounds of formula I, wherein Z is -NR¹²R¹³, are those wherein both R¹² and R¹³ are hydrogen.

[0041] Preferred compounds wherein Z is optionally substituted (C_1 - C_6)alkyl are those wherein the substituents are halo, hydroxy, (C_1 - C_6)alkyl, amino, (C_1 - C_6)alkylamino, $[(C_1-C_6)\text{alkyl}]_2\text{amino}$, (C_1 - C_6)alkoxy, (C_6 - C_{10})aryl, or (C_1 - C_9)heteroaryl; more preferably wherein said Z (C_1 - C_6)alkyl group is mono or disubstituted (except for halo), most preferably wherein said substituent is selected from hydroxy, (C_1 - C_4)alkyl, amino, (C_1 - C_2)alkylamino, $[(C_1-C_2)\text{alkyl}]_2\text{amino}$, (C_1 - C_3)alkoxy and phenyl.

[0042] Most preferred compounds of the present invention are those wherein X is -O- and Z is -OR¹¹.

[0043] Other preferred compounds of the present invention are those wherein X is -O- and Z is -NR₁₂R₁₃.

[0044] Another embodiment of the invention (referred to as the Alkyl or Aryl Q's) include compounds of formula I wherein Q is (C_1-C_6) alkyl, (C_6-C_{10}) aryl, (C_1-C_9) heteroaryl, (C_3-C_9) heterocyclic, (C_6-C_{10}) aryl (C_1-C_6) alkyl, (C_1-C_9) heteroaryl (C_1-C_6) alkyl, (C_3-C_9) heterocyclic (C_1-C_6) alkyl, (C_6-C_{10}) aryl (C_6-C_{10}) aryl, (C_6-C_{10}) aryl (C_1-C_9) heteroaryl, (C_6-C_{10}) aryl (C_3-C_9) heterocyclic, (C_1-C_9) heteroaryl (C_6-C_{10}) aryl, (C_1-C_9) heteroaryl (C_1-C_9) heteroaryl, (C_1-C_9) heteroaryl (C_3-C_9) heterocyclic, (C_3-C_9) heterocyclic (C_6-C_{10}) aryl, (C_1-C_9) heteroaryl (C_3-C_9) heterocyclic, (C_3-C_9) heterocyclic (C_3-C_9) heterocyclic.

[0045] Another embodiment of the invention (referred to as the Aryl-Ethers) include compounds of formula I wherein Q is $(C_6-C_{10})\text{aryloxy}(C_1-C_6)\text{alkyl}$, $(C_6-C_{10})\text{aryloxy}(C_6-C_{10})\text{aryl}$, $(C_6-C_{10})\text{aryloxy}(C_1-C_9)\text{heteroaryl}$, $(C_6-C_{10})\text{aryloxy}(C_3-C_9)\text{heterocyclic}$, $(C_1-C_9)\text{heteroaryloxy}(C_1-C_6)\text{alkyl}$, $(C_1-C_9)\text{heteroaryloxy}(C_6-C_{10})\text{aryl}$, $(C_1-C_9)\text{heteroaryloxy}(C_1-C_9)\text{heteroaryl}$, $(C_1-C_9)\text{heteroaryloxy}(C_3-C_9)\text{heterocyclic}$, $(C_3-C_9)\text{heterocyclic-O-(C_1-C_6)alkyl}$, $(C_3-C_9)\text{heterocyclic-O-(C_6-C_{10})aryl}$, $(C_3-C_9)\text{heterocyclic-O-(C_1-C_9)heteroaryl}$ or $(C_3-C_9)\text{heterocyclic-O-(C_1-C_9)heterocyclic}$.

[0046] Another embodiment of the invention (referred to as the Aryl-Alkyl-Ethers) include compounds of formula I wherein Q is $(C_6-C_{10})\text{aryl}(C_1-C_6)\text{alkoxy}(C_6-C_{10})\text{aryl}$, $(C_6-C_{10})\text{aryl}(C_1-C_6)\text{alkoxy}(C_1-C_9)\text{heteroaryl}$, $(C_6-C_{10})\text{aryl}(C_1-C_6)\text{alkoxy}(C_3-C_9)\text{heterocyclic}$, $(C_1-C_9)\text{heteroaryl}(C_1-C_6)\text{alkoxy}(C_6-C_{10})\text{aryl}$, $(C_1-C_9)\text{heteroaryl}(C_1-C_6)\text{alkoxy}(C_1-C_9)\text{heteroaryl}$, $(C_1-C_9)\text{heteroaryl}(C_1-C_6)\text{alkoxy}(C_3-C_9)\text{heterocyclic}$, $(C_3-C_9)\text{heterocyclic}(C_1-C_6)\text{alkoxy}(C_1-C_9)\text{heteroaryl}$ or $(C_3-C_9)\text{heterocyclic}(C_1-C_6)\text{alkoxy}(C_3-C_9)\text{heterocyclic}$.

[0047] Another embodiment of the invention (referred to as the Reverse-ethers) include compounds of formula I wherein Q is $(C_6-C_{10})\text{aryloxy}(C_1-C_6)\text{alkyl}(C_6-C_{10})\text{aryl}$, $(C_6-C_{10})\text{aryloxy}(C_1-C_6)\text{alkyl}(C_1-C_9)\text{heteroaryl}$, $(C_6-C_{10})\text{aryloxy}(C_1-C_6)\text{alkyl}(C_3-C_9)\text{heterocyclic}$, $(C_1-C_9)\text{heteroaryloxy}(C_1-C_6)\text{alkyl}(C_6-C_{10})\text{aryl}$, $(C_1-C_9)\text{heteroaryloxy}(C_1-C_6)\text{alkyl}(C_1-C_9)\text{heteroaryl}$, $(C_1-C_9)\text{heteroaryloxy}(C_1-C_6)\text{alkyl}(C_3-C_9)\text{heterocyclic}$, $(C_3-C_9)\text{heterocyclic-O-(C}_1-C_6)\text{alkyl}(C_6-C_{10})\text{aryl}$, $(C_3-C_9)\text{heterocyclic-O-(C}_1-C_6)\text{alkyl}(C_1-C_9)\text{heteroaryl}$ or $(C_3-C_9)\text{heterocyclic-O-(C}_1-C_6)\text{alkyl}(C_3-C_9)\text{heterocyclic}$.

[0049] Another embodiment of the invention (referred to as the Amino-aryls) include compounds of formula I wherein Q is $(C_6-C_{10})\text{aryl}-NH-(C_1-C_6)\text{alkyl}$, $(C_6-C_{10})\text{aryl}-NH-(C_6-C_{10})\text{aryl}$, $(C_6-C_{10})\text{aryl}-NH-(C_1-C_9)\text{heteroaryl}$, $(C_6-C_{10})\text{aryl}-NH-(C_3-C_9)\text{heterocyclic}$, $(C_1-C_9)\text{heteroaryl}-NH-(C_1-C_6)\text{alkyl}$, $(C_1-C_9)\text{heteroaryl}-NH-(C_6-C_{10})\text{aryl}$, $(C_1-C_9)\text{heteroaryl}$.

[0050] Preferred compounds of the invention wherein Q contains two or more pendant rings, are those compounds

wherein the rings are each connected in a para orientation, more preferably wherein the ring connected to the nucleus (i.e. the "X" containing ring) through the SO_2 group is substituted in the para orientation.

[0051] Other preferred compounds of the present invention are those wherein Q is $(\text{C}_6\text{-C}_{10})\text{aryl}(\text{C}_1\text{-C}_6)\text{alkoxy}(\text{C}_6\text{-C}_{10})\text{aryl}$, $(\text{C}_6\text{-C}_{10})\text{aryl}(\text{C}_1\text{-C}_6)\text{alkoxy}(\text{C}_1\text{-C}_9)\text{heteroaryl}$, $(\text{C}_1\text{-C}_9)\text{heteroaryl}(\text{C}_1\text{-C}_6)\text{alkoxy}(\text{C}_6\text{-C}_{10})\text{aryl}$, $(\text{C}_1\text{-C}_9)\text{heteroaryl}(\text{C}_1\text{-C}_6)\text{alkoxy}(\text{C}_1\text{-C}_9)\text{heteroaryl}$, optionally substituted by one or more, preferably one to three substituents per ring, most preferably one to three substituents on the terminal ring, wherein said substituent is selected from halo, $(\text{C}_1\text{-C}_6)$ alkyl, $(\text{C}_1\text{-C}_6)\text{alkoxy}$ or perfluoro($\text{C}_1\text{-C}_3$)alkyl.

[0052] Other preferred compounds of the present invention are those wherein Q is piperidinyl, piperazinyl, pyrrolidino, morpholinyl, thiomorpholinyl, $(\text{C}_6\text{-C}_{10})\text{aryl}\text{piperidinyl}$, $(\text{C}_1\text{-C}_9)\text{heteroaryl}\text{piperidinyl}$, $(\text{C}_6\text{-C}_{10})\text{aryloxy}\text{piperidinyl}$, $(\text{C}_1\text{-C}_9)\text{heteroaryl}\text{oxypiperidinyl}$, $(\text{C}_6\text{-C}_{10})\text{aryl}\text{piperazinyl}$ or $(\text{C}_1\text{-C}_9)\text{heteroaryl}\text{piperazinyl}$ optionally substituted by one or more, preferably one to three substituents per ring, most preferably one to three substituents on the terminal ring, wherein said substituent is selected from halo, $(\text{C}_1\text{-C}_6)$ alkyl, $(\text{C}_1\text{-C}_6)\text{alkoxy}$ or perfluoro($\text{C}_1\text{-C}_3$)alkyl.

[0053] Other preferred compounds of the present invention are those wherein Q is $(\text{C}_6\text{-C}_{10})\text{aryl}\text{methoxy}(\text{C}_6\text{-C}_{10})\text{aryl}$, $(\text{C}_6\text{-C}_{10})\text{aryl}\text{methoxy}(\text{C}_2\text{-C}_9)\text{heteroaryl}$, $(\text{C}_2\text{-C}_9)\text{heteroaryl}\text{methoxy}(\text{C}_6\text{-C}_{10})\text{aryl}$ or $(\text{C}_2\text{-C}_9)\text{heteroaryl}\text{methoxy}(\text{C}_2\text{-C}_9)\text{heteroaryl}$ optionally substituted by one or more, preferably one to three substituents per ring, most preferably one to three substituents on the terminal ring, wherein said substituent is selected from halo, $(\text{C}_1\text{-C}_6)$ alkyl, $(\text{C}_1\text{-C}_6)\text{alkoxy}$ or perfluoro($\text{C}_1\text{-C}_3$)alkyl.

[0054] More preferred compounds of the invention are those wherein Q is optionally substituted $(\text{C}_6\text{-C}_{10})\text{aryl}\text{methoxyphenyl}$, $(\text{C}_6\text{-C}_{10})\text{aryl}\text{methoxypyridyl}$, $(\text{C}_6\text{-C}_{10})\text{aryl}\text{methoxyfuryl}$, $(\text{C}_6\text{-C}_{10})\text{aryl}\text{methoxypyroyl}$, $(\text{C}_6\text{-C}_{10})\text{aryl}\text{methoxythienyl}$, $(\text{C}_6\text{-C}_{10})\text{aryl}\text{methoxyisothiazolyl}$, $(\text{C}_6\text{-C}_{10})\text{aryl}\text{methoxyimidazolyl}$, $(\text{C}_6\text{-C}_{10})\text{aryl}\text{methoxypyrazinyl}$, $(\text{C}_6\text{-C}_{10})\text{aryl}\text{methoxypyrimidyl}$, $(\text{C}_6\text{-C}_{10})\text{aryl}\text{methoxyquinolyl}$, $(\text{C}_6\text{-C}_{10})\text{aryl}\text{methoxypyrazolyl}$, $(\text{C}_6\text{-C}_{10})\text{aryl}\text{methoxyisoxazolyl}$, $(\text{C}_6\text{-C}_{10})\text{aryl}\text{methoxythiazolyl}$, $(\text{C}_6\text{-C}_{10})\text{aryl}\text{methoxyoxazolyl}$,

pyridylmethoxyphenyl, furylmethoxyphenyl, pyrrolylmethoxyphenyl, thietylmethoxyphethyl, isothiazolylmethoxyphenyl, imidazolylmethoxyphenyl, benzimidazolylmethoxyphenyl, tetrazolylmethoxyphenyl, pyrazinylmethoxyphenyl, pyrimidylmethoxyphenyl, quinolylmethoxyphenyl, isoquinolylmethoxyphenyl, benzofurylmethoxyphenyl, isobenzofurylmethoxyphenyl, benzothienylmethoxyphenyl, pyrazolylmethoxyphenyl, indolylmethoxyphenyl, isoindolylmethoxyphenyl, purinylmethoxyphenyl, carbazolylmethoxyphenyl, isoxazolylmethoxyphenyl, thiazolylmethoxyphenyl, oxazolylmethoxyphenyl, benzthiazolylmethoxyphenyl, benzoxazolylmethoxyphenyl,

pyridylmethoxypyridyl, pyridylmethoxyfuryl, pyridylmethoxypyroyl, pyridylmethoxythienyl, pyridylmethoxyisothiazolyl, pyridylmethoxyimidazolyl, pyridylmethoxypyrazinyl, pyridylmethoxypyrimidyl, pyridylmethoxyquinolyl, pyridylmethoxypyrazolyl, pyridylmethoxyisoxazolyl, pyridylmethoxythiazolyl, pyridylmethoxyoxazolyl,

furylmethoxypyridyl, furylmethoxyfuryl, furylmethoxypyroyl, furylmethoxythienyl, furylmethoxyisothiazolyl, furylmethoxyimidazolyl, furylmethoxypyrazinyl, furylmethoxypyrimidyl, furylmethoxyquinolyl, furylmethoxypyrazolyl, furylmethoxyisoxazolyl, furylmethoxythiazolyl, furylmethoxyoxazolyl,

pyrrolylmethoxypyridyl, pyrrolylmethoxyfuryl, pyrrolylmethoxypyroyl, pyrrolylmethoxythienyl, pyrrolylmethoxyisothiazolyl, pyrrolylmethoxyimidazolyl, pyrrolylmethoxypyrazinyl, pyrrolylmethoxypyrimidyl, pyrrolylmethoxyquinolyl, pyrrolylmethoxypyrazolyl, pyrrolylmethoxyisoxazolyl, pyrrolylmethoxythiazolyl, pyrrolylmethoxyoxazolyl,

thienylmethoxypyridyl, thienylmethoxyfuryl, thienylmethoxypyroyl, thienylmethoxythienyl, thienylmethoxyisothiazolyl, thienylmethoxyimidazolyl, thienylmethoxypyrazinyl, thienylmethoxypyrimidyl, thienylmethoxyquinolyl, thienylmethoxyisoxazolyl, thienylmethoxythiazolyl, thienylmethoxyoxazolyl,

pyrazinylmethoxypyridyl, pyrazinylmethoxyfuryl, pyrazinylmethoxypyroyl, pyrazinylmethoxythienyl, pyrazinylmethoxyisothiazolyl, pyrazinylmethoxyimidazolyl, pyrazinylmethoxypyrazinyl, pyrazinylmethoxypyrimidyl, pyrazinylmethoxyquinolyl, pyrazinylmethoxyisoxazolyl, pyrazinylmethoxythiazolyl, pyrazinylmethoxyoxazolyl,

pyrimidylmethoxypyridyl, pyrimidylmethoxyfuryl, pyrimidylmethoxypyroyl, pyrimidylmethoxythienyl, pyrimidylmethoxyisothiazolyl, pyrimidylmethoxyimidazolyl, pyrimidylmethoxypyrazinyl, pyrimidylmethoxypyrimidyl, pyrimidylmethoxyquinolyl, pyrimidylmethoxyisoxazolyl, pyrimidylmethoxythiazolyl, pyrimidylmethoxyoxazolyl,

thiazolylmethoxypyridyl, thiazolylmethoxyfuryl, thiazolylmethoxypyroyl, thiazolylmethoxythienyl, thiazolylmethoxyisothiazolyl, thiazolylmethoxyimidazolyl, thiazolylmethoxypyrazinyl, thiazolylmethoxypyrimidyl, thiazolylmethoxyquinolyl, thiazolylmethoxyisoxazolyl, thiazolylmethoxythiazolyl, thiazolylmethoxyoxazolyl, and

oxazolylmethoxypyridyl, oxazolylmethoxyfuryl, oxazolylmethoxypyroyl, oxazolylmethoxythienyl, oxazolylmethoxyisothiazolyl, oxazolylmethoxyimidazolyl, oxazolylmethoxypyrazinyl, oxazolylmethoxypyrimidyl, oxazolylmethoxyquinolyl, oxazolylmethoxyisoxazolyl, oxazolylmethoxythiazolyl or oxazolylmethoxyoxazolyl.

[0055] More preferred compounds of the invention are those wherein Q is optionally substituted $(\text{C}_6\text{-C}_{10})\text{aryl}\text{methoxyphenyl}$, $(\text{C}_6\text{-C}_{10})\text{aryl}\text{methoxypyridyl}$, $(\text{C}_6\text{-C}_{10})\text{aryl}\text{methoxyfuryl}$, $(\text{C}_6\text{-C}_{10})\text{aryl}\text{methoxypyroyl}$, $(\text{C}_6\text{-C}_{10})\text{aryl}\text{methoxythienyl}$, $(\text{C}_6\text{-C}_{10})\text{aryl}\text{methoxyisothiazolyl}$, $(\text{C}_6\text{-C}_{10})\text{aryl}\text{methoxyimidazolyl}$, $(\text{C}_6\text{-C}_{10})\text{aryl}\text{methoxypyrazinyl}$, $(\text{C}_6\text{-C}_{10})\text{aryl}\text{methoxypyrimidyl}$, $(\text{C}_6\text{-C}_{10})\text{aryl}\text{methoxyquinolyl}$, $(\text{C}_6\text{-C}_{10})\text{aryl}\text{methoxyisoxazolyl}$, $(\text{C}_6\text{-C}_{10})\text{aryl}\text{methoxythiazolyl}$, $(\text{C}_6\text{-C}_{10})\text{aryl}\text{methoxyoxazolyl}$,

5 pyridylmethoxyphenyl, furylmethoxyphenyl, pyrolylmethoxyphenyl, thienylmethoxyphenyl, isothiazolylmethoxyphenyl, imidazolylmethoxyphenyl, benzimidazolylmethoxyphenyl, tetrazolylmethoxyphenyl, pyrazinylmethoxyphenyl, pyrimidylmethoxyphenyl, quinolylmethoxyphenyl, isoquinolylmethoxyphenyl, benzofurylmethoxyphenyl, isobenzofurylmethoxyphenyl, benzothienylmethoxyphenyl, pyrazolylmethoxyphenyl, indolylmethoxyphenyl, isoindolylmethoxyphenyl, purinylmethoxyphenyl, carbazolylmethoxyphenyl, isoxazolylmethoxyphenyl, thiazolylmethoxyphenyl, oxazolylmethoxyphenyl, benzthiazolylmethoxyphenyl or benzoxazolylmethoxyphenyl.

[0056] More preferred compounds of the present invention are those wherein Q is optionally substituted (C_6 - C_{10}) arylmethoxyphenyl, pyridylmethoxyphenyl, furylmethoxyphenyl, pyrolylmethoxyphenyl, thienylmethoxyphenyl, isothiazolylmethoxyphenyl, imidazolylmethoxyphenyl, benzimidazolylmethoxyphenyl, tetrazolylmethoxyphenyl, pyrazinylmethoxyphenyl, pyrimidylmethoxyphenyl, quinolylmethoxyphenyl, isoquinolylmethoxyphenyl, benzofurylmethoxyphenyl, isobenzofurylmethoxyphenyl, benzothienylmethoxyphenyl, pyrazolylmethoxyphenyl, indolylmethoxyphenyl, isoindolylmethoxyphenyl, purinylmethoxyphenyl, carbazolylmethoxyphenyl, isoxazolylmethoxyphenyl, thiazolylmethoxyphenyl, oxazolylmethoxyphenyl, benzthiazolylmethoxyphenyl or benzoxazolylmethoxyphenyl.

[0057] More preferred compounds of the invention are those wherein Q is optionally substituted 4-((C_6 - C_{10})arylmethoxy-phenyl, 4-(pyridylmethoxy)-phenyl, 4-(thienylmethoxy)-phenyl, 4-(pyrazinylmethoxy)-phenyl, 4-(pyrimidylmethoxy)-phenyl, 4-(pyridazinylmethoxy)-phenyl, 4-(thiazolylmethoxy)-phenyl, or 4-(oxazolylmethoxy)-phenyl.

[0058] Most preferred compounds of the present invention are those wherein Q is 4-(C_6 - C_{10})aryl(methoxy)-phenyl optionally substituted by one or more, preferably one to three substituents per ring, most preferably one to three substituents on the terminal ring, wherein said substituents are independently selected from halo, (C_1 - C_6)alkyl, (C_1 - C_6)alkoxy or perfluoro(C_1 - C_3)alkyl.

[0059] Other more preferred compounds of the present invention are those wherein Q is 4-((C_6 - C_{10})aryl(methoxy)-(C_2 - C_9)heteroaryl optionally substituted by one or more, preferably one to three substituents per ring, most preferably one to three substituents on the terminal ring, wherein said substituents are independently selected from halo, (C_1 - C_6)alkyl, (C_1 - C_6)alkoxy or perfluoro(C_1 - C_3)alkyl.

[0060] Other more preferred compounds of the present invention are those wherein Q is 4-((C_2 - C_9)heteroaryl(methoxy)-phenyl optionally substituted by one or more, preferably one to three substituents per ring, most preferably one to three substituents on the terminal ring, wherein said substituents are independently selected from halo, (C_1 - C_6)alkyl, (C_1 - C_6)alkoxy or perfluoro(C_1 - C_3)alkyl.

[0061] Other more preferred compounds of the present invention are those wherein Q is 4-((C_2 - C_9)heteroaryl(methoxy)-(C_2 - C_9)heteroaryl optionally substituted by one or more, preferably one to three substituents per ring, most preferably one to three substituents on the terminal ring, wherein said substituents are independently selected from halo, (C_1 - C_6)alkyl, (C_1 - C_6)alkoxy or perfluoro(C_1 - C_3)alkyl.

[0062] Other preferred compounds of the present invention are those wherein R¹, R², R⁵ and R⁶ are each independently selected from the group consisting of hydrogen, (C_1 - C_6)alkyl, (C_2 - C_6)alkenyl, (C_2 - C_6)alkynyl, perfluoro(C_1 - C_6)alkyl, (C_6 - C_{10})aryl, (C_1 - C_9)heteroaryl, (C_3 - C_6)cycloalkyl, (C_3 - C_9)heterocyclic, (C_1 - C_6)alkyl(C=O)-, (C_1 - C_6)alkoxy-(C=O)-, -CO₂H, H₂N-(C=O)-, (C_1 - C_6)alkyl-NH-(C=O)-, and [(C_1 - C_6)alkyl]₂-N-(C=O)-; wherein each of said (C_1 - C_6)alkyl groups are each independently optionally substituted by one to three groups selected from halo, trifluoromethyl, hydroxy, amino, (C_1 - C_6)alkoxy, (C_6 - C_{10})aryl, (C_1 - C_9)heteroaryl, (C_3 - C_6)cycloalkyl, (C_3 - C_9)heterocyclic, (C_1 - C_6)alkyl-(C=O)-NH-, (C_1 - C_6)alkyl-(C=O)-O-, (C_1 - C_6)alkylamino or ((C_1 - C_6)alkyl)₂amino; more preferably wherein R¹, R², R⁵ and R⁶ are each independently selected from the group consisting of hydrogen, (C_1 - C_6)alkyl, (C_2 - C_6)alkenyl, perfluoro(C_1 - C_6)alkyl, (C_1 - C_6)alkyl(C=O)-, (C_1 - C_6)alkoxy-(C=O)-, (C_1 - C_6)alkyl-NH-(C=O)-, and [(C_1 - C_6)alkyl]₂-N-(C=O)-; wherein each of said (C_1 - C_6)alkyl groups are each independently optionally substituted by one to three groups selected from halo, trifluoromethyl, hydroxy, amino, (C_1 - C_6)alkoxy, (C_6 - C_{10})aryl, (C_1 - C_9)heteroaryl, (C_3 - C_6)cycloalkyl, (C_3 - C_9)heterocyclic, (C_1 - C_6)alkyl-(C=O)-NH-, (C_1 - C_6)alkyl-(C=O)-O-, (C_1 - C_6)alkylamino or ((C_1 - C_6)alkyl)₂amino; more preferably wherein R¹, R², R⁵ and R⁶ are each independently selected from the group consisting of hydrogen, (C_1 - C_6)alkyl and (C_2 - C_6)alkenyl; wherein said (C_1 - C_6)alkyl groups are each independently optionally substituted by one to three groups (more preferably one to two groups) selected from halo, hydroxy, amino, (C_1 - C_6)alkoxy or (C_6 - C_{10})aryl; most preferably wherein R¹, R², R⁵ and R⁶ are each independently selected from the group consisting of hydrogen or (C_1 - C_4)alkyl.

[0063] Other preferred compounds of the present invention are those wherein R⁷ and R⁸ are each independently selected from the group consisting of hydrogen, hydroxy, halo, (C_1 - C_6)alkyl, (C_2 - C_6)alkenyl, (C_2 - C_6)alkynyl, amino, (C_1 - C_6)alkylamino, [(C_1 - C_6)alkyl]₂amino, (C_1 - C_6)alkoxy, perfluoro(C_1 - C_6)alkyl, perfluoro(C_1 - C_6)alkoxy, (C_3 - C_6)cycloalkyl, (C_6 - C_{10})aryl, (C_3 - C_9)heterocyclic, (C_1 - C_9)heteroaryl, (C_1 - C_6)alkyl(C=O)-, (C_1 - C_6)alkyl(C=O)-NH-, (C_1 - C_6)alkyl(C=O)-O-, (C_1 - C_6)alkoxy-(C=O)-, -CO₂H, H₂N-(C=O)-, (C_1 - C_6)alkyl-NH-(C=O)-, and [(C_1 - C_6)alkyl]₂-N-(C=O)-; more preferably wherein R⁷ and R⁸ are each independently selected from the group consisting of hydrogen, hydroxy, halo, (C_1 - C_6)alkyl, (C_2 - C_6)alkenyl, amino, (C_1 - C_6)alkylamino, [(C_1 - C_6)alkyl]₂amino, (C_1 - C_6)alkoxy, perfluoro(C_1 - C_6)alkyl and perfluoro(C_1 - C_6)alkoxy; most preferably wherein R⁷ and R⁸ are each independently selected from the group consisting of hydrogen, hydroxy, (C_1 - C_4)alkyl, amino, (C_1 - C_4)alkoxy, trifluoromethyl and trifluoromethoxy.

[0064] Other preferred compounds of the present invention are those wherein at least one of R¹ and R², R⁵ and R⁶ or R⁷ and R⁸ are taken together to form a carbonyl group or an optionally substituted (C₃-C₆)cycloalkyl ring; more preferably wherein one of R¹ and R², R⁵ and R⁶ or R⁷ and R⁸ is taken together to form a carbonyl group.

5 [0065] Other compounds of the present invention are those wherein one of R⁵ and R⁷, R⁵ and R⁸, R⁶ and R⁷ or R⁶ and R⁸ are taken together to form an optionally substituted (C₄-C₆)cycloalkyl ring, preferably cis fused.

[0066] Other more preferred compounds of the present invention are those wherein R¹ or R² are hydrogen.

[0067] Other more preferred compounds of the present invention are those wherein at least one of R¹ or R² is other than hydrogen.

10 [0068] Other more preferred compounds of the present invention are those wherein at least one of R¹-R⁶ is (C₁-C₆)alkyl, more preferably methyl or ethyl.

[0069] Other compounds of the present invention are those wherein at least one of R¹-R⁶ is other than hydrogen or (C₁-C₆)alkyl.

[0070] Other more preferred compounds of the present invention are those wherein at least one of R¹-R² is (C₁-C₆)alkyl, preferably methyl or ethyl.

15 [0071] Other more preferred compounds of the present invention are those wherein R¹ is hydrogen or (C₁-C₆)alkyl, preferably hydrogen, methyl or ethyl.

[0072] Other more preferred compounds of the present invention are those wherein R² is hydrogen or (C₁-C₆)alkyl, preferably hydrogen, methyl or ethyl.

20 [0073] Other more preferred compounds of the present invention are those wherein R³ is hydrogen or (C₁-C₆)alkyl, preferably hydrogen, methyl or ethyl.

[0074] Other more preferred compounds of the present invention are those wherein R⁵ is hydrogen or (C₁-C₆)alkyl, preferably hydrogen, methyl or ethyl.

[0075] Other more preferred compounds of the present invention are those wherein R⁶ is hydrogen or (C₁-C₆)alkyl, preferably hydrogen, methyl or ethyl.

25 [0076] Other more preferred compounds of the present invention are those wherein R⁷ is hydrogen or (C₁-C₆)alkyl, preferably hydrogen, methyl or ethyl.

[0077] Other more preferred compounds of the present invention are those wherein R⁸ is (C₁-C₆)alkyl, preferably methyl or ethyl.

[0078] Other more preferred compounds of the present invention are those wherein R⁴ is hydrogen.

30 [0079] Other more preferred compounds of the present invention are those wherein R¹ and R² are each (C₁-C₆)alkyl, preferably methyl or ethyl.

[0080] Other more preferred compounds of the present invention are those wherein R⁵ and R⁶ are each (C₁-C₆)alkyl, preferably methyl or ethyl.

35 [0081] Other more preferred compounds of the present invention are those wherein R⁷ and R⁸ are each (C₁-C₆)alkyl, preferably methyl or ethyl.

[0082] Most preferred compounds of the invention are those wherein R¹-R⁸ are each hydrogen, or R¹ or R² are each methyl or ethyl.

[0083] Specific most preferred compounds of the present invention are selected from the group consisting of:

40 4-[4-(4-Fluoro-2-methyl-benzyl)oxy]-benzenesulfonyl]-3-hydroxy-tetrahydro-pyran-3-carboxylic acid hydroxyamide;

4-[4-(3-Chloro-benzyl)oxy]-benzenesulfonyl]-3-hydroxy-tetrahydro-pyran-3-carboxylic acid hydroxyamide;

4-[4-(4-Chloro-benzyl)oxy]-benzenesulfonyl]-3-hydroxy-tetrahydro-pyran-3-carboxylic acid hydroxyamide;

4-[4-(2-Chloro-benzyl)oxy]-benzenesulfonyl]-3-hydroxy-tetrahydro-pyran-3-carboxylic acid hydroxyamide;

45 4-[4-(3-Fluoro-benzyl)oxy]-benzenesulfonyl]-3-hydroxy-tetrahydro-pyran-3-carboxylic acid hydroxyamide;

3-Hydroxy-4-[4-(2-methyl-benzyl)oxy]-benzenesulfonyl]-tetrahydro-pyran-3-carboxylic acid hydroxyamide; and

4-[4-(4-Fluoro-2-methyl-benzyl)oxy]-benzenesulfonyl]-3-hydroxy-tetrahydro-pyran-3-carboxylic acid hydroxy-

amide.

50 [0084] Other specific pyran compounds of the invention are:

4-(2'-Chloro-biphenyl-4-sulfonyl)-3-hydroxy-tetrahydro-pyran-3-carboxylic acid hydroxyamide,

4-(3'-Chloro-biphenyl-4-sulfonyl)-3-hydroxy-tetrahydro-pyran-3-carboxylic acid hydroxyamide,

4-(4'-Chloro-biphenyl-4-sulfonyl)-3-hydroxy-tetrahydro-pyran-3-carboxylic acid hydroxyamide,

55 3-Hydroxy-4-(4'-methyl-biphenyl-4-sulfonyl)-tetrahydro-pyran-3-carboxylic acid hydroxyamide,

3-Hydroxy-4-(3'-methyl-biphenyl-4-sulfonyl)-tetrahydro-pyran-3-carboxylic acid hydroxyamide,

3-Hydroxy-4-(2'-methyl-biphenyl-4-sulfonyl)-tetrahydro-pyran-3-carboxylic acid hydroxyamide,

4-(2'-Fluoro-biphenyl-4-sulfonyl)-3-hydroxy-tetrahydro-pyran-3-carboxylic acid hydroxyamide,

4-[4-(3-Fluoro-phenoxy)-piperidine-1-sulfonyl]-3-hydroxy-tetrahydro-pyran-3-carboxylic acid hydroxyamide,
 4-[4-(4-Fluoro-phenoxy)-piperidine-1-sulfonyl]-3-hydroxy-tetrahydro-pyran-3-carboxylic acid hydroxyamide,
 3-Hydroxy-4-(4-o-tolyloxy-piperidine-1-sulfonyl)-tetrahydro-pyran-3-carboxylic acid hydroxyamide,
 3-Hydroxy-4-(4-m-tolyloxy-piperidine-1-sulfonyl)-tetrahydro-pyran-3-carboxylic acid hydroxyamide,
 5 3-Hydroxy-4-(4-p-tolyloxy-piperidine-1-sulfonyl)-tetrahydro-pyran-3-carboxylic acid hydroxyamide,
 3-Hydroxy-4-[4-(2-methoxy-phenoxy)-piperidine-1-sulfonyl]-tetrahydro-pyran-3-carboxylic acid hydroxyamide,
 3-Hydroxy-4-[4-(3-methoxy-phenoxy)-piperidine-1-sulfonyl]-tetrahydro-pyran-3-carboxylic acid hydroxyamide,
 3-Hydroxy-4-[4-(4-methoxy-phenoxy)-piperidine-1-sulfonyl]-tetrahydro-pyran-3-carboxylic acid hydroxyamide,
 3-Hydroxy-4-(4-phenoxy-piperidine-1-sulfonyl)-tetrahydro-pyran-3-carboxylic acid hydroxyamide,
 10 4-(4-Benzyl-oxo-piperidine-1-sulfonyl)-3-hydroxy-tetrahydro-pyran-3-carboxylic acid hydroxyamide,
 4-[4-(2-Chloro-benzyl-oxo)-piperidine-1-sulfonyl]-3-hydroxy-tetrahydro-pyran-3-carboxylic acid hydroxyamide,
 4-[4-(3-Chloro-benzyl-oxo)-piperidine-1-sulfonyl]-3-hydroxy-tetrahydro-pyran-3-carboxylic acid hydroxyamide,
 4-[4-(4-Chloro-benzyl-oxo)-piperidine-1-sulfonyl]-3-hydroxy-tetrahydro-pyran-3-carboxylic acid hydroxyamide,
 4-[4-(2-Fluoro-benzyl-oxo)-piperidine-1-sulfonyl]-3-hydroxy-tetrahydro-pyran-3-carboxylic acid hydroxyamide,
 15 4-[4-(3-Fluoro-benzyl-oxo)-piperidine-1-sulfonyl]-3-hydroxy-tetrahydro-pyran-3-carboxylic acid hydroxyamide,
 4-[4-(4-Fluoro-benzyl-oxo)-piperidine-1-sulfonyl]-3-hydroxy-tetrahydro-pyran-3-carboxylic acid hydroxyamide,
 3-Hydroxy-4-[4-(2-methyl-benzyl-oxo)-piperidine-1-sulfonyl]-tetrahydro-pyran-3-carboxylic acid hydroxyamide,
 3-Hydroxy-4-[4-(3-methyl-benzyl-oxo)-piperidine-1-sulfonyl]-tetrahydro-pyran-3-carboxylic acid hydroxyamide,
 20 3-Hydroxy-4-[4-(4-methyl-benzyl-oxo)-piperidine-1-sulfonyl]-tetrahydro-pyran-3-carboxylic acid hydroxyamide,
 3-Hydroxy-4-[4-(2-methoxy-benzyl-oxo)-piperidine-1-sulfonyl]-tetrahydro-pyran-3-carboxylic acid hydroxyamide,
 3-Hydroxy-4-[4-(3-methoxy-benzyl-oxo)-piperidine-1-sulfonyl]-tetrahydro-pyran-3-carboxylic acid hydroxyamide,
 3-Hydroxy-4-[4-(4-methoxy-benzyl-oxo)-piperidine-1-sulfonyl]-tetrahydro-pyran-3-carboxylic acid hydroxyamide,
 25 3-Hydroxy-4-[4-(pyridin-2-ylmethoxy)-piperidine-1-sulfonyl]-tetrahydro-pyran-3-carboxylic acid hydroxyamide,
 4-[4-(2,6-Dimethyl-pyridin-4-ylmethoxy)-piperidine-1-sulfonyl]-3-hydroxy-tetrahydro-pyran-3-carboxylic acid hydroxyamide,
 4-[4-(2,6-Dimethyl-pyridin-4-ylmethoxy)-benzenesulfonyl]-3-hydroxy-tetrahydro-pyran-3-carboxylic acid hydroxyamide,
 30 3-Hydroxy-4-[4-(pyridin-4-ylmethoxy)-benzenesulfonyl]-tetrahydro-pyran-3-carboxylic acid hydroxyamide,
 3-Hydroxy-4-[4-(pyridin-3-ylmethoxy)-benzenesulfonyl]-tetrahydro-pyran-3-carboxylic acid hydroxyamide,
 3-Hydroxy-4-[4-(pyridin-2-ylmethoxy)-benzenesulfonyl]-tetrahydro-pyran-3-carboxylic acid hydroxyamide,
 4-(4-Benzyl-oxo-benzenesulfonyl)-3-hydroxy-tetrahydro-pyran-3-carboxylic acid hydroxyamide,
 4-[4-(2-Chloro-benzyl-oxo)-benzenesulfonyl]-3-hydroxy-tetrahydro-pyran-3-carboxylic acid hydroxyamide,
 35 4-[4-(3-Chloro-benzyl-oxo)-benzenesulfonyl]-3-hydroxy-tetrahydro-pyran-3-carboxylic acid hydroxyamide,
 4-[4-(4-Chloro-benzyl-oxo)-benzenesulfonyl]-3-hydroxy-tetrahydro-pyran-3-carboxylic acid hydroxyamide,
 4-[4-(2-Fluoro-benzyl-oxo)-benzenesulfonyl]-3-hydroxy-tetrahydro-pyran-3-carboxylic acid hydroxyamide,
 4-[4-(3-Fluoro-benzyl-oxo)-benzenesulfonyl]-3-hydroxy-tetrahydro-pyran-3-carboxylic acid hydroxyamide,
 4-[4-(4-Fluoro-benzyl-oxo)-benzenesulfonyl]-3-hydroxy-tetrahydro-pyran-3-carboxylic acid hydroxyamide,
 40 3-Hydroxy-4-[4-(2-methyl-benzyl-oxo)-benzenesulfonyl]-tetrahydro-pyran-3-carboxylic acid hydroxyamide,
 3-Hydroxy-4-[4-(3-methyl-benzyl-oxo)-benzenesulfonyl]-tetrahydro-pyran-3-carboxylic acid hydroxyamide,
 3-Hydroxy-4-[4-(4-methyl-benzyl-oxo)-benzenesulfonyl]-tetrahydro-pyran-3-carboxylic acid hydroxyamide,
 3-Hydroxy-4-[4-(2-methoxy-benzyl-oxo)-benzenesulfonyl]-tetrahydro-pyran-3-carboxylic acid hydroxyamide,
 3-Hydroxy-4-[4-(3-methoxy-benzyl-oxo)-benzenesulfonyl]-tetrahydro-pyran-3-carboxylic acid hydroxyamide, and
 45 3-Hydroxy-4-[4-(4-methoxy-benzyl-oxo)-benzenesulfonyl]-tetrahydro-pyran-3-carboxylic acid hydroxyamide.

[0085] Other specific piperidine compounds of the invention are:

50 4-(2'-Chloro-biphenyl-4-sulfonyl)-3-hydroxy-piperidin-3-carboxylic acid hydroxyamide,
 4-(3'-Chloro-biphenyl-4-sulfonyl)-3-hydroxy-piperidin-3-carboxylic acid hydroxyamide,
 4-(4'-Chloro-biphenyl-4-sulfonyl)-3-hydroxy-piperidin-3-carboxylic acid hydroxyamide,
 3-Hydroxy-4-(4'-methyl-biphenyl-4-sulfonyl)-piperidin-3-carboxylic acid hydroxyamide,
 3-Hydroxy-4-(3'-methyl-biphenyl-4-sulfonyl)-piperidin-3-carboxylic acid hydroxyamide,
 3-Hydroxy-4-(2'-methyl-biphenyl-4-sulfonyl)-piperidin-3-carboxylic acid hydroxyamide,
 55 4-(2'-Fluoro-biphenyl-4-sulfonyl)-3-hydroxy-piperidin-3-carboxylic acid hydroxyamide,
 4-(3'-Fluoro-biphenyl-4-sulfonyl)-3-hydroxy-piperidin-3-carboxylic acid hydroxyamide,
 4-(4'-Fluoro-biphenyl-4-sulfonyl)-3-hydroxy-piperidin-3-carboxylic acid hydroxyamide,
 3-Hydroxy-4-(4-pyridin-4-yl-benzenesulfonyl)-piperidin-3-carboxylic acid hydroxyamide,

3-Hydroxy-4-(4-pyridin-3-yl-benzenesulfonyl)-piperidin-3-carboxylic acid hydroxyamide,
 3-Hydroxy-4-(4-pyridin-2-yl-benzenesulfonyl)-piperidin-3-carboxylic acid hydroxyamide,
 3-Hydroxy-4-(4'-methoxy-biphenyl-4-sulfonyl)-piperidin-3-carboxylic acid hydroxyamide,
 3-Hydroxy-4-(3'-methoxy-biphenyl-4-sulfonyl)-piperidin-3-carboxylic acid hydroxyamide,
 5 3-Hydroxy-4-(2'-methoxy-biphenyl-4-sulfonyl)-piperidin-3-carboxylic acid hydroxyamide,
 4-(Biphenyl-4-sulfonyl)-3-hydroxy-piperidin-3-carboxylic acid hydroxyamide,
 3-Hydroxy-4-(4-phenyl-piperidine-1-sulfonyl)-piperidin-3-carboxylic acid hydroxyamide,
 4-[4-(2-Chloro-phenyl)-piperidine-1-sulfonyl]-3-hydroxy-piperidin-3-carboxylic acid hydroxyamide,
 10 4-[4-(3-Chloro-phenyl)-piperidine-1-sulfonyl]-3-hydroxy-piperidin-3-carboxylic acid hydroxyamide,
 4-[4-(4-Chloro-phenyl)-piperidine-1-sulfonyl]-3-hydroxy-piperidin-3-carboxylic acid hydroxyamide,
 3-Hydroxy-4-(4-o-tolyl-piperidine-1-sulfonyl)-piperidin-3-carboxylic acid hydroxyamide,
 15 3-Hydroxy-4-(4-m-tolyl-piperidine-1-sulfonyl)-piperidin-3-carboxylic acid hydroxyamide,
 3-Hydroxy-4-(4-p-tolyl-piperidine-1-sulfonyl)-piperidin-3-carboxylic acid hydroxyamide,
 4-[4-(2-Fluoro-phenyl)-piperidine-1-sulfonyl]-3-hydroxy-piperidin-3-carboxylic acid hydroxyamide,
 15 4-[4-(3-Fluoro-phenyl)-piperidine-1-sulfonyl]-3-hydroxy-piperidin-3-carboxylic acid hydroxyamide,
 4-[4-(4-Fluoro-phenyl)-piperidine-1-sulfonyl]-3-hydroxy-piperidin-3-carboxylic acid hydroxyamide,
 3-Hydroxy-4-[4-(2-methoxy-phenyl)-piperidine-1-sulfonyl]-piperidin-3-carboxylic acid hydroxyamide,
 3-Hydroxy-4-[4-(4-methoxy-phenyl)-piperidine-1-sulfonyl]-piperidin-3-carboxylic acid hydroxyamide,
 20 3-Hydroxy-4-[4-(3-methoxy-phenyl)-piperidine-1-sulfonyl]-piperidin-3-carboxylic acid hydroxyamide,
 3-Hydroxy-4-(3',4',5',6'-tetrahydro-2'H-[2,4']bipyridinyl-1'-sulfonyl)-piperidin-3-carboxylic acid hydroxyamide,
 3-Hydroxy-4-(3',4',5',6'-tetrahydro-2'H-[3,4']bipyridinyl-1'-sulfonyl)-piperidin-3-carboxylic acid hydroxyamide,
 4-(2',6'-Dimethyl-3,4,5,6-tetrahydro-2H-[4,4']bipyridinyl-1-sulfonyl)-3-hydroxy-piperidin-3-carboxylic acid hydroxyamide,
 25 4-[4-(2,6-Dimethyl-pyridin-4-yl)-benzenesulfonyl]-3-hydroxy-piperidin-3-carboxylic acid hydroxyamide,
 3-Hydroxy-4-(4-phenoxy-benzenesulfonyl)-piperidin-3-carboxylic acid hydroxyamide,
 4-[4-(2-Chloro-phenoxy)-benzenesulfonyl]-3-hydroxy-piperidin-3-carboxylic acid hydroxyamide,
 4-[4-(3-Chloro-phenoxy)-benzenesulfonyl]-3-hydroxy-piperidin-3-carboxylic acid hydroxyamide,
 30 4-[4-(4-Chloro-phenoxy)-benzenesulfonyl]-3-hydroxy-piperidin-3-carboxylic acid hydroxyamide,
 3-Hydroxy-4-(4-o-tolyl-oxo-benzenesulfonyl)-piperidin-3-carboxylic acid hydroxyamide,
 3-Hydroxy-4-(4-m-tolyl-oxo-benzenesulfonyl)-piperidin-3-carboxylic acid hydroxyamide,
 3-Hydroxy-4-(4-p-tolyl-oxo-benzenesulfonyl)-piperidin-3-carboxylic acid hydroxyamide,
 4-[4-(2-Fluoro-phenoxy)-benzenesulfonyl]-3-hydroxy-piperidin-3-carboxylic acid hydroxyamide,
 35 4-[4-(3-Fluoro-phenoxy)-benzenesulfonyl]-3-hydroxy-piperidin-3-carboxylic acid hydroxyamide,
 4-[4-(4-Fluoro-phenoxy)-benzenesulfonyl]-3-hydroxy-piperidin-3-carboxylic acid hydroxyamide,
 3-Hydroxy-4-[4-(2-methoxy-phenoxy)-benzenesulfonyl]-piperidin-3-carboxylic acid hydroxyamide,
 3-Hydroxy-4-[4-(3-methoxy-phenoxy)-benzenesulfonyl]-piperidin-3-carboxylic acid hydroxyamide,
 3-Hydroxy-4-[4-(4-methoxy-phenoxy)-benzenesulfonyl]-piperidin-3-carboxylic acid hydroxyamide,
 40 3-Hydroxy-4-[4-(pyridin-2-yloxy)-benzenesulfonyl]-piperidin-3-carboxylic acid hydroxyamide,
 3-Hydroxy-4-[4-(pyridin-3-yloxy)-benzenesulfonyl]-piperidin-3-carboxylic acid hydroxyamide,
 3-Hydroxy-4-[4-(pyridin-4-yloxy)-benzenesulfonyl]-piperidin-3-carboxylic acid hydroxyamide,
 4-[4-(2,6-Dimethyl-pyridin-4-yloxy)-benzenesulfonyl]-3-hydroxy-piperidin-3-carboxylic acid hydroxyamide,
 4-[4-(2,6-Dimethyl-pyridin-4-yloxy)-piperidine-1-sulfonyl]-3-hydroxy-piperidin-3-carboxylic acid hydroxyamide,
 45 3-Hydroxy-4-[4-(pyridin-4-yloxy)-piperidine-1-sulfonyl]-piperidin-3-carboxylic acid hydroxyamide,
 3-Hydroxy-4-[4-(pyridin-3-yloxy)-piperidine-1-sulfonyl]-piperidin-3-carboxylic acid hydroxyamide,
 3-Hydroxy-4-[4-(pyridin-2-yloxy)-piperidine-1-sulfonyl]-piperidin-3-carboxylic acid hydroxyamide,
 4-[4-(2-Chloro-phenoxy)-piperidine-1-sulfonyl]-3-hydroxy-piperidin-3-carboxylic acid hydroxyamide,
 4-[4-(3-Chloro-phenoxy)-piperidine-1-sulfonyl]-3-hydroxy-piperidin-3-carboxylic acid hydroxyamide,
 50 4-[4-(4-Chloro-phenoxy)-piperidine-1-sulfonyl]-3-hydroxy-piperidin-3-carboxylic acid hydroxyamide,
 4-[4-(2-Fluoro-phenoxy)-piperidine-1-sulfonyl]-3-hydroxy-piperidin-3-carboxylic acid hydroxyamide,
 4-[4-(3-Fluoro-phenoxy)-piperidine-1-sulfonyl]-3-hydroxy-piperidin-3-carboxylic acid hydroxyamide,
 4-[4-(4-Fluoro-phenoxy)-piperidine-1-sulfonyl]-3-hydroxy-piperidin-3-carboxylic acid hydroxyamide,
 3-Hydroxy-4-(4-o-tolyl-oxo-piperidine-1-sulfonyl)-piperidin-3-carboxylic acid hydroxyamide,
 3-Hydroxy-4-(4-m-tolyl-oxo-piperidine-1-sulfonyl)-piperidin-3-carboxylic acid hydroxyamide,
 55 3-Hydroxy-4-(4-p-tolyl-oxo-piperidine-1-sulfonyl)-piperidin-3-carboxylic acid hydroxyamide,
 3-Hydroxy-4-[4-(2-methoxy-phenoxy)-piperidine-1-sulfonyl]-piperidin-3-carboxylic acid hydroxyamide,
 3-Hydroxy-4-[4-(3-methoxy-phenoxy)-piperidine-1-sulfonyl]-piperidin-3-carboxylic acid hydroxyamide,
 3-Hydroxy-4-[4-(4-methoxy-phenoxy)-piperidine-1-sulfonyl]-piperidin-3-carboxylic acid hydroxyamide,

3-Hydroxy-4-(4-phenoxy-piperidine-1-sulfonyl)-piperidin-3-carboxylic acid hydroxyamide,
 4-(4-Benzyl-oxo-piperidine-1-sulfonyl)-3-hydroxy-piperidin-3-carboxylic acid hydroxyamide,
 4-[4-(2-Chloro-benzyl-oxo)-piperidine-1-sulfonyl]-3-hydroxy-piperidin-3-carboxylic acid hydroxyamide,
 4-[4-(3-Chloro-benzyl-oxo)-piperidine-1-sulfonyl]-3-hydroxy-piperidin-3-carboxylic acid hydroxyamide,
 5 4-[4-(4-Chloro-benzyl-oxo)-piperidine-1-sulfonyl]-3-hydroxy-piperidin-3-carboxylic acid hydroxyamide,
 4-[4-(2-Fluoro-benzyl-oxo)-piperidine-1-sulfonyl]-3-hydroxy-piperidin-3-carboxylic acid hydroxyamide,
 4-[4-(3-Fluoro-benzyl-oxo)-piperidine-1-sulfonyl]-3-hydroxy-piperidin-3-carboxylic acid hydroxyamide,
 4-[4-(4-Fluoro-benzyl-oxo)-piperidine-1-sulfonyl]-3-hydroxy-piperidin-3-carboxylic acid hydroxyamide,
 10 3-Hydroxy-4-[4-(2-methyl-benzyl-oxo)-piperidine-1-sulfonyl]-piperidin-3-carboxylic acid hydroxyamide,
 3-Hydroxy-4-[4-(3-methyl-benzyl-oxo)-piperidine-1-sulfonyl]-piperidin-3-carboxylic acid hydroxyamide,
 3-Hydroxy-4-[4-(4-methyl-benzyl-oxo)-piperidine-1-sulfonyl]-piperidin-3-carboxylic acid hydroxyamide,
 3-Hydroxy-4-[4-(2-methoxy-benzyl-oxo)-piperidine-1-sulfonyl]-piperidin-3-carboxylic acid hydroxyamide,
 15 3-Hydroxy-4-[4-(3-methoxy-benzyl-oxo)-piperidine-1-sulfonyl]-piperidin-3-carboxylic acid hydroxyamide,
 3-Hydroxy-4-[4-(4-methoxy-benzyl-oxo)-piperidine-1-sulfonyl]-piperidin-3-carboxylic acid hydroxyamide,
 3-Hydroxy-4-[4-(pyridin-2-ylmethoxy)-piperidine-1-sulfonyl]-piperidin-3-carboxylic acid hydroxyamide,
 3-Hydroxy-4-[4-(pyridin-3-ylmethoxy)-piperidine-1-sulfonyl]-piperidin-3-carboxylic acid hydroxyamide,
 20 3-Hydroxy-4-[4-(pyridin-4-ylmethoxy)-piperidine-1-sulfonyl]-piperidin-3-carboxylic acid hydroxyamide,
 4-[4-(2,6-Dimethyl-pyridin-4-ylmethoxy)-piperidine-1-sulfonyl]-3-hydroxy-piperidin-3-carboxylic acid hydroxyamide,
 4-[4-(2,6-Dimethyl-pyridin-4-ylmethoxy)-benzenesulfonyl]-3-hydroxy-piperidin-3-carboxylic acid hydroxyamide,
 3-Hydroxy-4-[4-(pyridin-4-ylmethoxy)-benzenesulfonyl]-piperidin-3-carboxylic acid hydroxyamide,
 3-Hydroxy-4-[4-(pyridin-3-ylmethoxy)-benzenesulfonyl]-piperidin-3-carboxylic acid hydroxyamide,
 25 4-[4-(2-Chloro-benzyl-oxo)-benzenesulfonyl]-3-hydroxy-piperidin-3-carboxylic acid hydroxyamide,
 4-[4-(3-Chloro-benzyl-oxo)-benzenesulfonyl]-3-hydroxy-piperidin-3-carboxylic acid hydroxyamide,
 4-[4-(4-Chloro-benzyl-oxo)-benzenesulfonyl]-3-hydroxy-piperidin-3-carboxylic acid hydroxyamide,
 4-[4-(2-Fluoro-benzyl-oxo)-benzenesulfonyl]-3-hydroxy-piperidin-3-carboxylic acid hydroxyamide,
 30 4-[4-(3-Fluoro-benzyl-oxo)-benzenesulfonyl]-3-hydroxy-piperidin-3-carboxylic acid hydroxyamide,
 4-[4-(4-Fluoro-benzyl-oxo)-benzenesulfonyl]-3-hydroxy-piperidin-3-carboxylic acid hydroxyamide,
 3-Hydroxy-4-[4-(2-methyl-benzyl-oxo)-benzenesulfonyl]-piperidin-3-carboxylic acid hydroxyamide,
 3-Hydroxy-4-[4-(3-methyl-benzyl-oxo)-benzenesulfonyl]-piperidin-3-carboxylic acid hydroxyamide,
 35 3-Hydroxy-4-[4-(4-methyl-benzyl-oxo)-benzenesulfonyl]-piperidin-3-carboxylic acid hydroxyamide,
 3-Hydroxy-4-[4-(2-methoxy-benzyl-oxo)-benzenesulfonyl]-piperidin-3-carboxylic acid hydroxyamide,
 3-Hydroxy-4-[4-(3-methoxy-benzyl-oxo)-benzenesulfonyl]-piperidin-3-carboxylic acid hydroxyamide, and
 3-Hydroxy-4-[4-(4-methoxy-benzyl-oxo)-benzenesulfonyl]-piperidin-3-carboxylic acid hydroxyamide.

[0086] Other specific compounds of the invention are:

40 4-[4-(4-Fluoro-2-methyl-benzyl-oxo)-benzenesulfonyl]-3-hydroxy-2,2-dimethyl-tetrahydro-pyran-3-carboxylic acid hydroxyamide,
 4-[4-(4-Fluoro-2-chloro-benzyl-oxo)-benzenesulfonyl]-3-hydroxy-2,2-dimethyl-tetrahydro-pyran-3-carboxylic acid hydroxyamide,
 4-[4-(2,4-Dichloro-benzyl-oxo)-benzenesulfonyl]-3-hydroxy-2,2-dimethyl-tetrahydro-pyran-3-carboxylic acid hydroxyamide,
 45 4-[4-(5-Fluoro-2-methyl-benzyl-oxo)-benzenesulfonyl]-3-hydroxy-2,2-dimethyl-tetrahydro-pyran-3-carboxylic acid hydroxyamide,
 4-[4-(4-Fluoro-benzyl-oxo)-benzenesulfonyl]-3-hydroxy-2,2-dimethyl-tetrahydro-pyran-3-carboxylic acid hydroxyamide,
 50 3-Amino-4-[4-(4-fluoro-2-methyl-benzyl-oxo)-benzenesulfonyl]-tetrahydro-pyran-3-carboxylic acid hydroxyamide,
 3-Amino-4-[4-(4-fluoro-2-chloro-benzyl-oxo)-benzenesulfonyl]-tetrahydro-pyran-3-carboxylic acid hydroxyamide,
 3-Amino-4-[4-(2,4-dichloro-benzyl-oxo)-benzenesulfonyl]-tetrahydro-pyran-3-carboxylic acid hydroxyamide,
 3-Amino-4-[4-(5-fluoro-2-methyl-benzyl-oxo)-benzenesulfonyl]-tetrahydro-pyran-3-carboxylic acid hydroxyamide,
 55 3-Amino-4-[4-(4-fluoro-benzyl-oxo)-benzenesulfonyl]-tetrahydro-pyran-3-carboxylic acid hydroxyamide,
 4-[4-(4-Fluoro-2-methyl-benzyl-oxo)-benzenesulfonyl]-3-methoxy-tetrahydro-pyran-3-carboxylic acid hydroxyamide,
 4-[4-(4-Fluoro-2-chloro-benzyl-oxo)-benzenesulfonyl]-3-methoxy-tetrahydro-pyran-3-carboxylic acid hydroxy-

4-[4-(4-Fluoro-2-chloro-benzyl)-benzenesulfonyl]-3-ethoxy-piperidin-3-carboxylic acid hydroxyamide,
 4-[4-(2,4-Dichloro-benzyl)-benzenesulfonyl]-3-ethoxy-piperidin-3-carboxylic acid hydroxyamide,
 4-[4-(5-Fluoro-2-methyl-benzyl)-benzenesulfonyl]-3-ethoxy-piperidin-3-carboxylic acid hydroxyamide,
 4-[4-(4-Fluoro-benzyl)-benzenesulfonyl]-3-ethoxy-piperidin-3-carboxylic acid hydroxyamide,
 5 3-Amino-4-[4-(4-fluoro-2-methyl-benzyl)-benzenesulfonyl]-2,2-dimethyl-piperidin-3-carboxylic acid hydroxy-
 amide,
 3-Amino-4-[4-(4-fluoro-2-chloro-benzyl)-benzenesulfonyl]-2,2-dimethyl-piperidin-3-carboxylic acid hydroxy-
 amide,
 10 3-Amino-4-[4-(2,4-dichloro-benzyl)-benzenesulfonyl]-2,2-dimethyl-piperidin-3-carboxylic acid hydroxy-
 amide,
 3-Amino-4-[4-(5-fluoro-2-methyl-benzyl)-benzenesulfonyl]-2,2-dimethyl-piperidin-3-carboxylic acid hydroxy-
 amide,
 15 3-Amino-4-[4-(4-fluoro-benzyl)-benzenesulfonyl]-2,2-dimethyl-piperidin-3-carboxylic acid hydroxy-
 amide,
 4-[4-(2,4-Dichloro-benzyl)-benzenesulfonyl]-3-methyl-2,2-dimethyl-piperidin-3-carboxylic acid hydroxy-
 amide,
 4-[4-(5-Fluoro-2-methyl-benzyl)-benzenesulfonyl]-3-methyl-2,2-dimethyl-piperidin-3-carboxylic acid hydroxy-
 amide,
 20 4-[4-(4-Fluoro-benzyl)-benzenesulfonyl]-3-methyl-2,2-dimethyl-piperidin-3-carboxylic acid hydroxy-
 amide,
 4-[4-(4-Fluoro-2-methyl-benzyl)-benzenesulfonyl]-3-hydroxy-2-oxo-piperidin-3-carboxylic acid hydroxy-
 amide,
 4-[4-(4-Fluoro-2-chloro-benzyl)-benzenesulfonyl]-3-hydroxy-2-oxo-piperidin-3-carboxylic acid hydroxy-
 amide,
 4-[4-(2,4-Dichloro-benzyl)-benzenesulfonyl]-3-hydroxy-2-oxo-piperidin-3-carboxylic acid hydroxy-
 amide,
 4-[4-(5-Fluoro-2-methyl-benzyl)-benzenesulfonyl]-3-hydroxy-2-oxo-piperidin-3-carboxylic acid hydroxy-
 amide,
 25 and
 4-[4-(4-Fluoro-benzyl)-benzenesulfonyl]-3-hydroxy-2-oxo-piperidin-3-carboxylic acid hydroxy-
 amide.

[0087] The present invention also relates to a pharmaceutical composition for the treatment of a condition selected from the group consisting of arthritis (including osteoarthritis and rheumatoid arthritis), inflammatory bowel disease, 30 Crohn's disease, emphysema, acute respiratory distress syndrome, asthma, chronic obstructive pulmonary disease, Alzheimer's disease, organ transplant toxicity, cachexia, allergic reactions, allergic contact hypersensitivity, cancer (such as solid tumor cancer including colon cancer, breast cancer, lung cancer and prostate cancer and hematopoietic malignancies including leukemias and lymphomas), tissue ulceration, restenosis, periodontal disease, epidermolysis bullosa, osteoporosis, loosening of artificial joint implants, atherosclerosis (including atherosclerotic plaque rupture), 35 aortic aneurysm (including abdominal aortic aneurysm and brain aortic aneurysm), congestive heart failure, myocardial infarction, stroke, cerebral ischemia, head trauma, spinal cord injury, neuro-degenerative disorders (acute and chronic), autoimmune disorders, Huntington's disease, Parkinson's disease, migraine, depression, peripheral neuropathy, pain, cerebral amyloid angiopathy, nootropic or cognition enhancement, amyotrophic lateral sclerosis, multiple sclerosis, ocular angiogenesis, corneal injury, macular degeneration, abnormal wound healing, burns, diabetes, tumor invasion, 40 tumor growth, tumor metastasis, corneal scarring, scleritis, AIDS, sepsis and septic shock in a mammal, including a human, comprising an amount of a compound of formula I or a pharmaceutically acceptable salt thereof effective in such treatments and a pharmaceutically acceptable carrier.

[0088] The present invention also relates to a pharmaceutical composition for the treatment of diseases characterized by metalloproteinase activity (preferably MMP-13) and other diseases characterized by mammalian reprolysin activity (preferably Aggrecanase activity most preferably Aggrecanase activity) in a mammal, including a human, comprising an amount of a compound of formula I or a pharmaceutically acceptable salt thereof effective in such treatments and a pharmaceutically acceptable carrier.

[0089] The present invention also relates to a pharmaceutical composition for the inhibition of (a) matrix metalloproteinases or other metalloproteinases involved in matrix degradation, or (b) a mammalian reprolysin (such as aggrecanase or ADAM's TS-1, 10, 12, 15 and 17, most preferably Aggrecanase) in a mammal, including a human, comprising an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

[0090] The present invention also relates to a method for treating a condition selected from the group consisting of arthritis (including osteoarthritis and rheumatoid arthritis), inflammatory bowel disease, Crohn's disease, emphysema, 55 acute respiratory distress syndrome, asthma, chronic obstructive pulmonary disease, Alzheimer's disease, organ transplant toxicity, cachexia, allergic reactions, allergic contact hypersensitivity, cancer (such as solid tumor cancer including colon cancer, breast cancer, lung cancer and prostate cancer and hematopoietic malignancies including leukemias and lymphomas), tissue ulceration, restenosis, periodontal disease, epidermolysis bullosa, osteoporosis, loosening of

artificial joint implants, atherosclerosis (including atherosclerotic plaque rupture), aortic aneurysm (including abdominal aortic aneurysm and brain aortic aneurysm), congestive heart failure, myocardial infarction, stroke, cerebral ischemia, head trauma, spinal cord injury, neuro-degenerative disorders (acute and chronic), autoimmune disorders, Huntington's disease, Parkinson's disease, migraine, depression, peripheral neuropathy, pain, cerebral amyloid angiopathy, noot-

5 ropic or cognition enhancement, amyotrophic lateral sclerosis, multiple sclerosis, ocular angiogenesis, corneal injury, macular degeneration, abnormal wound healing, burns, diabetes, tumor invasion, tumor growth, tumor metastasis, corneal scarring, scleritis, AIDS, sepsis and septic shock in a mammal, including a human, comprising administering to said mammal an amount of a compound of formula I or a pharmaceutically acceptable salt thereof effective in treating such a condition.

10 [0091] The present invention also relates to the treatment of diseases characterized by matrix metalloproteinase activity (preferably MMP-13 activity) and other diseases characterized by mammalian reprotoxin activity (preferably Aggrecanase activity) in a mammal, including a human, comprising administering to said mammal an amount of a compound of formula I or a pharmaceutically acceptable salt thereof effective in treating such a condition.

15 [0092] The present invention also relates to a method for the inhibition of (a) matrix metalloproteinases or other metalloproteinases involved in matrix degradation, or (b) a mammalian reprotoxin (such as aggrecanase or ADAM's TS-1, 10, 12, 15 and 17, preferably Aggrecanase) in a mammal, including a human, comprising administering to said mammal an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof.

20 [0093] The term "treating", as used herein, refers to reversing, alleviating, inhibiting the progress of, or preventing the disorder or condition to which such term applies, or one or more symptoms of such disorder or condition. The term "treatment", as used herein, refers to the act of treating, as "treating" is defined immediately above.

25 [0094] This invention also encompasses pharmaceutical compositions containing prodrugs of compounds of the formula I. This invention also encompasses methods of treating or preventing disorders that can be treated or prevented by the inhibition of matrix metalloproteinases or the inhibition of mammalian reprotoxin comprising administering prodrugs of compounds of the formula I. Compounds of formula I having free amino, amido, hydroxy, hydroxamic acid or carboxylic groups can be converted into prodrugs. Prodrugs include compounds wherein an amino acid residue, or a polypeptide chain of two or more (e.g., two, three or four) amino acid residues which are covalently joined through peptide bonds to free amino, hydroxy or carboxylic acid groups of compounds of formula I. The amino acid residues include the 20 naturally occurring amino acids commonly designated by three letter symbols and also include, 4-hydroxyproline, hydroxylysine, demosine, isodemosine, 3-methylhistidine, norvalin, beta-alanine, gamma-aminobutyric acid, citrulline, homocysteine, homoserine, ornithine and methionine sulfone. Prodrugs also include compounds wherein carbonates, carbamates, amides and esters which are covalently bonded to the above substituents of formula I through the carbonyl carbon prodrug sidechain.

30 [0095] One of ordinary skill in the art will appreciate that the compounds of the invention are useful in treating a diverse array of diseases. One of ordinary skill in the art will also appreciate that when using the compounds of the invention in the treatment of a specific disease that the compounds of the invention may be combined with various existing therapeutic agents used for that disease.

35 [0096] For the treatment of rheumatoid arthritis, the compounds of the invention may be combined with agents such as TACE inhibitors, TNF- α inhibitors such as anti-TNF monoclonal antibodies and TNF receptor immunoglobulin molecules (such as Enbrel \circledR), COX-2 inhibitors, low dose methotrexate, lefunimide, hydroxychloroquine, d-penicillamine, auranofin or parenteral or oral gold.

40 [0097] The compounds of the invention can also be used in combination with existing therapeutic agents for the treatment of osteoarthritis. Suitable agents to be used in combination include standard non-steroidal anti-inflammatory agents (hereinafter NSAID's) such as piroxicam, diclofenac, propionic acids such as naproxen, flubiprofen, fenoprofen, ketoprofen and ibuprofen, fenamates such as mefenamic acid, indomethacin, sulindac, apazone, pyrazolones such as phenylbutazone, salicylates such as aspirin, COX-2 inhibitors such as celecoxib, valdecoxib, paracoxib and rofecoxib, analgesics and intraarticular therapies such as corticosteroids and hyaluronic acids such as hyalgan and synvisc.

45 [0098] The compounds of the present invention may also be used in combination with anticancer agents such as endostatin and angiostatin or cytotoxic drugs such as adriamycin, daunomycin, cis-platinum, etoposide, taxol, taxotere and alkaloids, such as vincristine, and antimetabolites such as methotrexate.

50 [0099] The compounds of the present invention may also be used in combination with cardiovascular agents such as calcium channel blockers, lipid lowering agents such as statins, fibrates, beta-blockers, ACE inhibitors, Angiotensin-2 receptor antagonists and platelet aggregation inhibitors.

55 [0100] The compounds of the present invention may also be used in combination with CNS agents such as antidepressants (such as sertraline), anti-Parkinsonian drugs (such as deprenyl, L-dopa, requip, mirapex, MAOB inhibitors such as selegiline and rasagiline, COMT inhibitors such as Tasmar, A-2 inhibitors, dopamine reuptake inhibitors, NMDA antagonists, Nicotine agonists, Dopamine agonists and inhibitors of neuronal nitric oxide synthase), and anti-Alzheimer's drugs such as donepezil, tacrine, COX-2 Inhibitors, propentofylline or metryfonate.

[0101] The compounds of the present invention may also be used in combination with osteoporosis agents such as

roloxiene, droloxiene or fosomax and immunosuppressant agents such as FK-506 and rapamycin.

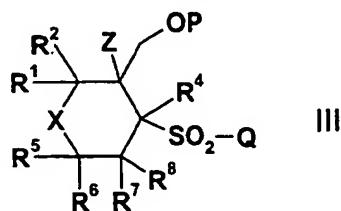
Detailed Description of the Invention

5 [0102] The following reaction Schemes illustrate the preparation of the compounds of the present invention. Unless otherwise indicated R¹-R¹⁵, X, Z and Q in the reaction Schemes and the discussion that follow are defined as above.

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SCHEME 1

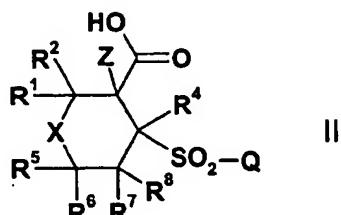
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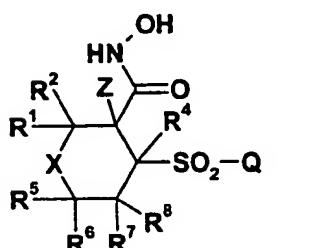
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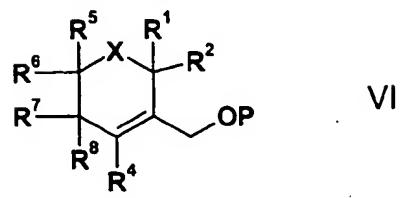
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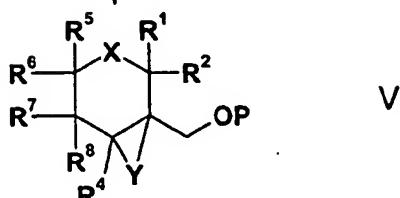
SCHEME 2

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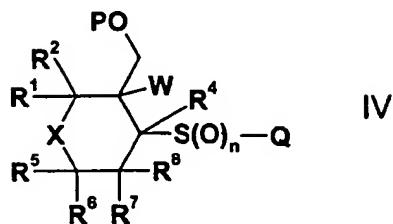
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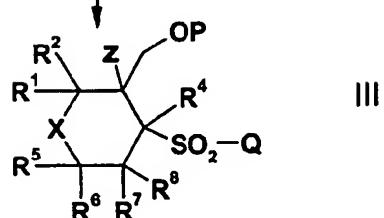


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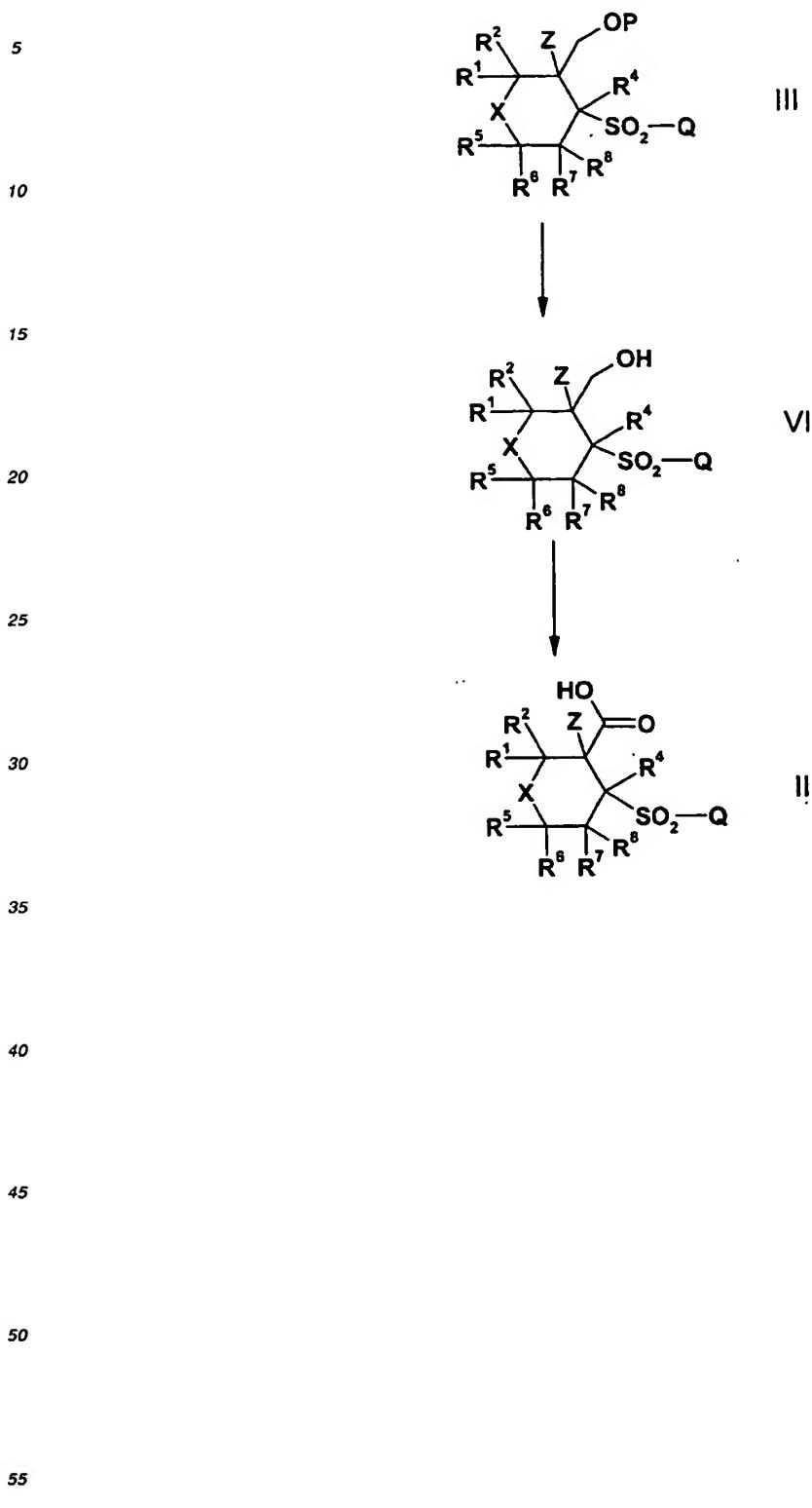
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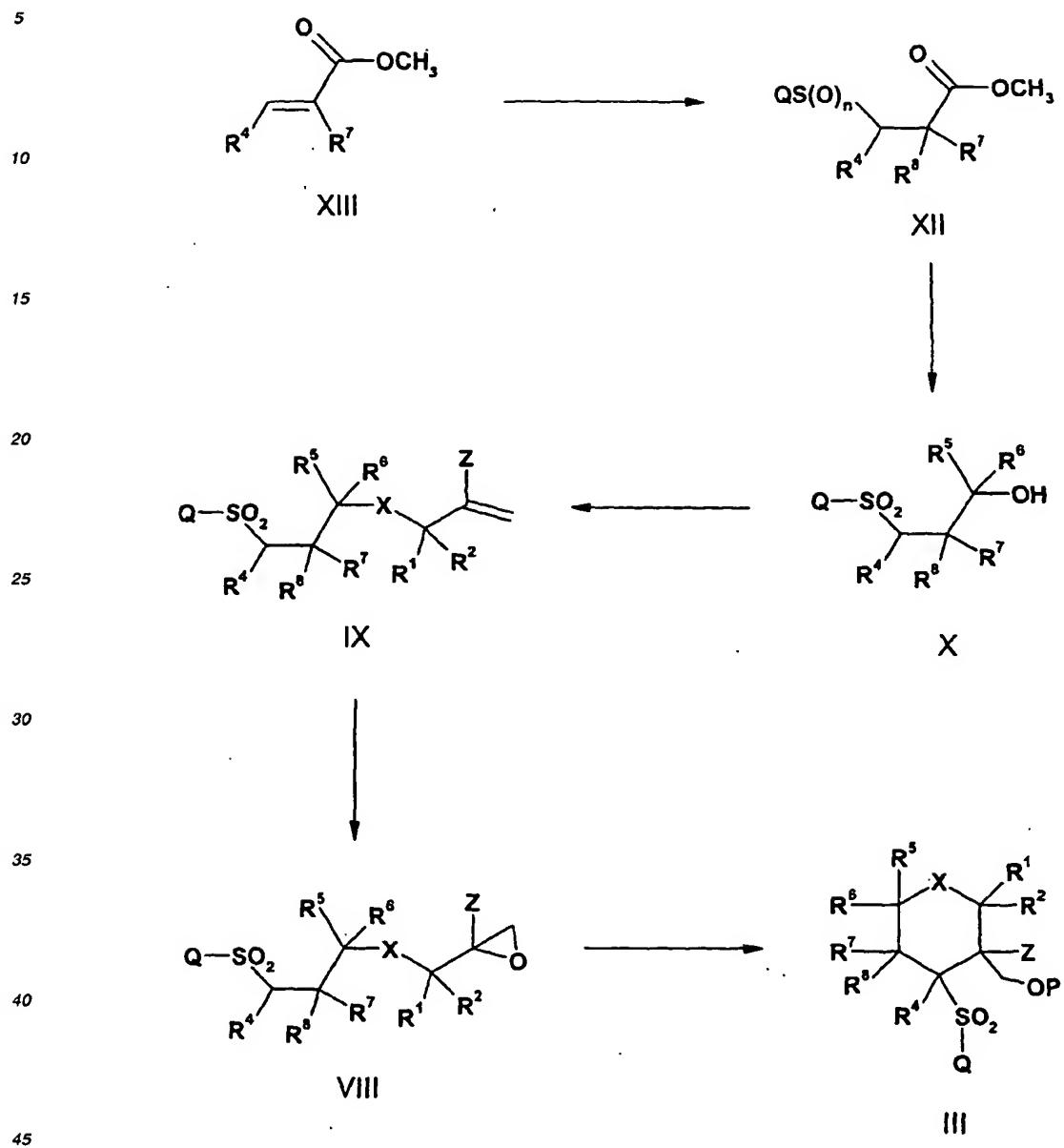


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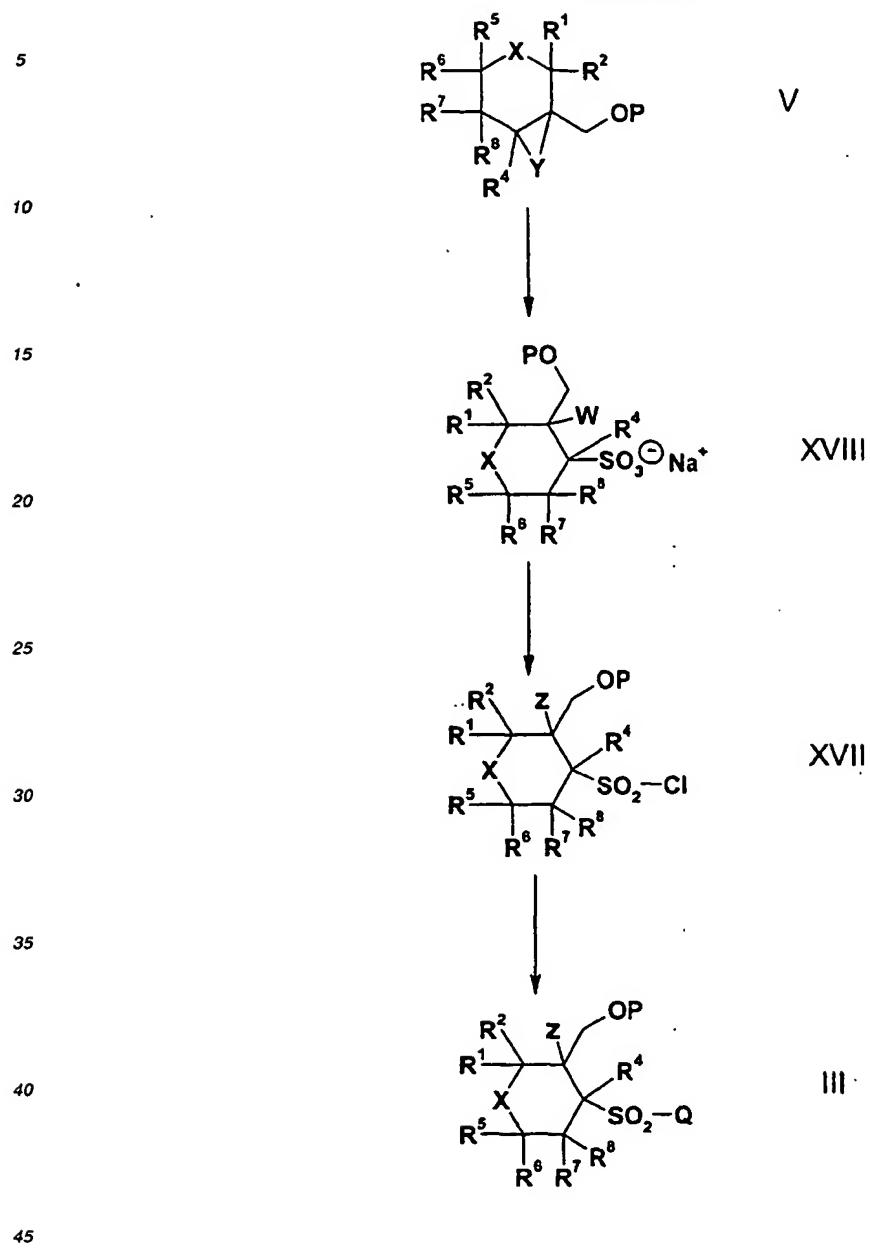
SCHEME 3



Scheme 4



Scheme 5



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Scheme 6

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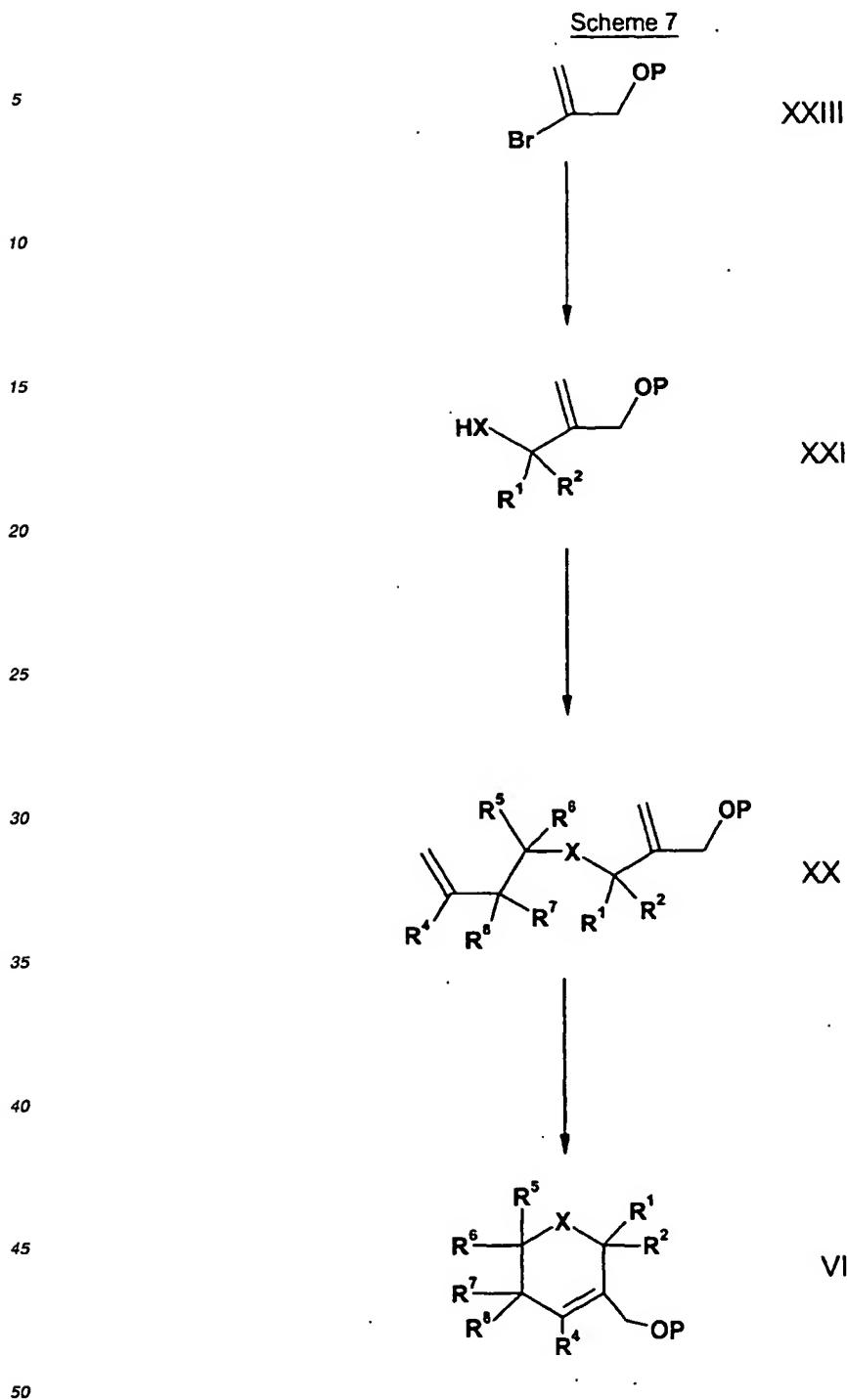
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Scheme 7



[0103] Scheme I refers to preparation of compounds of the formula I. Compounds of the formula I possess specific stereochemistry about the chiral hydroxamic acid carbon and sulfonyl carbon. The stereochemistry of the final product of formula I is determined by the stereochemistry at the epoxidation or aziridination step in Scheme 2. One of ordinary skill in the art will understand that after opening the epoxide or aziridine that subsequent intermediates may be epimerized so as to produce stereoisomeric mixtures that can be separated into individual stereoisomers, such as enantiomers or diastereomers, by methods well known to those skilled in the art.

[0104] Referring to Scheme 1, the compound of formula I is prepared from the carboxylic acid of formula II by treatment with an activating agent such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide and 1-hydroxybenztriazole in a polar solvent, such as N,N-dimethylformamide, followed by the addition of hydroxylamine to the reaction mixture after a time period between about 15 minutes to about 1 hour, preferably about 30 minutes. The aforesaid reaction is conducted at a temperature of about 0°C to about 50°C preferably about 20°C to about 23°C. The hydroxylamine is preferably generated *in situ* from a salt form, such as hydroxylamine hydrochloride, in the presence of a base, such as triethylamine.

[0105] Alternatively the compound of formula I can be prepared from a compound of formula II by reaction with a protected derivative of hydroxylamine or its salt form, where the hydroxyl group is protected as a tert-butyl, benzyl, allyl or 2-trimethylsilylethyl ether. Removal of the hydroxyl protecting group is carried out by hydrogenolysis for a benzyl protecting group (5% palladium on barium sulfate is the preferred catalyst) or treatment with a strong acid, such as trifluoroacetic acid, for a tert-butyl protecting group. The allyl protecting group may be removed by treatment with triethylamine and formic acid in the presence of catalytic tetrakis(triphenylphosphine) palladium(0) or tributyltinhydride and acetic acid in the presence of catalytic bis(triphenylphosphine) palladium(II)chloride. The 2-trimethylsilylethyl ether may be removed by reaction with a strong acid such as trifluoroacetic acid or by reaction with a fluoride source such as boron trifluoride etherate.

[0106] The reaction of a compound of formula II with hydroxylamine, a salt of hydroxylamine, a protected derivative of hydroxylamine or a salt of a protected derivative of hydroxylamine may also be carried out in the presence of (benztriazol-1-yloxy)tris(dimethylamino)-phosphonium hexafluorophosphate and a base such as triethylamine in an inert solvent, such as methylene chloride. The reaction mixture is stirred at a temperature between about 0°C to about 50°C, preferably room temperature, for a time period between about 1 hour to about 3 days, preferably about 1 day.

[0107] Another procedure for converting a compound of formula II to a compound of formula I is to react the compound of formula II with O-benzylhydroxylamine hydrochloride in the presence of (benztriazol-1-yloxy)tris(dimethylamino)-phosphonium hexafluorophosphate and triethylamine using methylene chloride as solvent. Subsequent removal of the O-benzyl protecting group to afford a compound of formula I is then carried out by hydrogenolysis under 3. atmospheres hydrogen at room temperature using 5% palladium on barium sulfate as a catalyst. The preferred solvent is methanol. The reaction time may vary from about 1 hour to about 2 days (8 hours is preferred).

[0108] Another alternative procedure for converting a compound of formula II to a compound of formula I is to react the compound of formula II with oxalyl chloride in methylene chloride in the presence of a catalytic amount of DMF for 16 hours. The resulting acid chloride is reacted at 0°C with N, O- bis trimethylsilyl hydroxylamine formed by reacting hydroxylamine hydrochloride with chlorotrimethyl-silane in pyridine at 0°C to room temperature. The product of formula I is obtained after a few hours reaction at about 0°C to about 20-23°C (i.e. room temperature) followed by an acidic aqueous workup which removes all trimethyl silyl residues.

[0109] In certain instances, it is preferred to obtain the compound of formula I by reaction of hydroxylamine, a salt of hydroxylamine, a protected derivative of hydroxylamine or a salt of a protected derivative of hydroxylamine with an activated ester equivalent of formula II. The reaction is carried out in an inert solvent, such as N,N-dimethyl-formamide at a temperature ranging from about 20-23°C (i.e. room temperature) to about 80°C, preferably about 60°C for a time period of about 1 hour to about 2 days. If a protected derivative of hydroxylamine or a salt of a protected derivative of hydroxylamine is used, removal of the protecting group is carried out as described above. The activated ester equivalent derivative of formula II is obtained by treatment of the compound of formula II with (benztriazol-1-yloxy)tris(dimethylamino)-phosphonium hexafluorophosphate and a base such as triethylamine in an inert solvent, such as methylene chloride. The reaction mixture is stirred at a temperature between about 0°C to about 50°C, preferably room temperature, for a time period between about 1 hour to about 3 days, preferably about 1 day.

[0110] A compound of the formula II, wherein Z is -OR¹¹, >NR¹²R¹³ or optionally substituted alkyl (suitably protected where appropriate) and R¹¹, R¹² and R¹³ are each hydrogen, may be prepared from a compound of the formula III, wherein wherein Z is -OR¹¹, >NR¹²R¹³ or optionally substituted alkyl (suitably protected where appropriate) and R¹¹, R¹² and R¹³ are each hydrogen and P is hydrogen, by treatment with a suitable oxidant, such as Jones Reagent or under other known conditions employing an alkali metal chlorite salt, preferably sodium chlorite in the presence of a suitable catalyst, such as a mixture of 2,2,6,6-tetramethyl-1-piperidinyloxy free radical (TEMPO) and sodium hypochlorite in a pH 7 buffered aqueous solution, with an appropriate aprotic polar co-solvent, preferably acetonitrile, from about 0°C to about 50°C, for about 4 to about 12 hours.

[0111] A compound of the formula II, wherein Z is -OR¹¹ or -NR¹²R¹³ and R¹¹ is other than hydrogen or at least one of R¹² and R¹³ is other than hydrogen can be prepared by the methods of Scheme 3.

[0112] A compound of the formula III, wherein Z is -OR¹¹ or -NR¹²R¹³ and R¹¹, R¹² and R¹³ are each hydrogen can be prepared according to the methods of Scheme 2. Compounds of the formula III, wherein Z is optionally substituted alkyl can be prepared according to the methods of Scheme 4.

[0113] Scheme 2 refers to the preparation of compounds of the formula III, wherein Z is -OR¹¹ or -NR¹²R¹³ and R¹¹, R¹² and R¹³ are each hydrogen and P is hydrogen or a protecting group. Compounds of the formula III can be converted

into compounds of the formula I according to the methods of Scheme 1.

[0114] Referring to Scheme 2, a compound of the formula III, wherein Z is -OR¹¹ or -NR¹²R¹³ and R¹¹, R¹² and R¹³ are each hydrogen and P is hydrogen, may be prepared from a compound of the formula III, wherein Z is -OR¹¹ or >NR¹²R¹³ and R¹¹, R¹² and R¹³ are each hydrogen and P is a protecting group, by removal of the protecting group.

5 Suitable protecting groups, including methods for their formation and cleavage, are described in detail in Greene and Wuts, "Protective Groups in Organic Synthesis" (Wiley Interscience, 2nd Ed.) (1991), see Chapter 2, incorporated herein by reference. When the protecting group is a silyl ether (such as *t*-butyl-dimethyl silyl ether), the reaction is carried out in a solvent such as THF, acetonitrile or methylene chloride with an excess of a fluoride source such as tetrabutyl ammonium fluoride, hydrogen fluoride in pyridine, boron trifluoride etherate, or cesium fluoride, preferably 10 tetrabutyl ammonium fluoride in THF or in a solvent such as wet THF or wet methanol with an excess of a protic acid such as dilute hydrochloric acid, acetic acid or toluene sulfonic acid, preferably dilute hydrochloric acid. The reaction mixture is stirred at a temperature of from about 0°C to about 80°C, preferably about 20°C (room temperature) for a time period of about 10 minutes to about 2 days, preferably about 1 hour.

[0115] A compound of the formula III, wherein Z is -OR¹¹, R¹¹ is hydrogen and P is a protecting group, may be 15 prepared from a compound of the formula IV, wherein W is -OR¹¹, R¹¹ is hydrogen, P is a protecting group and n is zero, by treatment with a suitable oxidant such as a peroxide or peroxyacid, preferably peroxyacetic acid, in the presence of a suitable buffer salt, such as sodium acetate in a polar solvent such as methylene chloride at a temperature from about -20°C to about 50°C for a period from about 2 hours to about 4 hours.

[0116] A compound of the formula III, wherein Z is -NR¹²R¹³ and R¹² and R¹³ are each hydrogen and P is protecting 20 group such as a silyl ether (such as *t*-butyl-dimethyl silyl ether), may be prepared from a compound of the formula IV, wherein W is -NHR¹⁴ and R¹⁴ is alkyl-O-(C=O)- and P is a protecting group and n is 2, by treatment with a suitable strong base, such as an alkoxide base, preferably potassium hydroxide, in a polar aprotic solvent such as an alcohol water mixture, at a temperature range of about 50°C to about 120°C, for a period from about 12 to about 48 hours.

[0117] Alternatively, a compound of the formula III, wherein Z is -NR¹²R¹³ and R¹² and R¹³ are each hydrogen and 25 P is protecting group such as a silyl ether (such as *t*-butyl-dimethyl silyl ether), may be prepared from a compound of the formula IV, wherein W is -NHR¹⁴, R¹⁴ is -(SO₂)-aryl and n is 2, by employment of a dissolving metal reduction, using an appropriate alkali metal such as sodium metal in liquid ammonia ethanol solution at a temperature of about -33°C to about 50°C, for a period from about 1 hour to about 3 hours.

[0118] A compound of the formula IV, wherein W is -NHR¹⁴ and R¹⁴ is alkyl-O-(C=O)- or -(SO₂)-aryl, P is a protecting 30 group such as a silyl ether (such as *t*-butyl-dimethyl silyl ether) and n is 2, may be prepared from a compound of the formula IV, wherein W is -NHR¹⁴ and R¹⁴ is alkyl-O-(C=O)- or -(SO₂)-aryl, P is a protecting group such as a silyl ether (such as *t*-butyl-dimethyl silyl ether) and n is zero, by treatment with a suitable oxidant such as a peroxide or peroxyacid, preferably peroxyacetic acid, in the presence of a suitable buffer salt, such as sodium acetate in a polar solvent such as methylene chloride at a temperature from about -20°C to about 50°C for a period from about 2 hours to about 4 hours.

[0119] The compound of the formula IV, wherein W is -OR¹¹ or -NHR¹⁴ and R¹¹ is hydrogen and R¹⁴ is alkyl-O-(C=O)- or -(SO₂)-aryl, P is hydrogen or a protecting group such as a silyl ether (such as *t*-butyl-dimethyl silyl ethers) and n is zero, may be prepared from a compound of the formula V, wherein Y is -O- or >NR¹⁴ and R¹⁴ is alkyl-O-(C=O)- or aryl(SO₂)- and P is a protecting group or hydrogen, by treatment with a compound of formula QSH in the presence of a suitable base, such as an alkali metal hydride, tertiary amine base or alkoxide base, preferably sodium hydride or 40 triethylamine, in a polar solvent such as acetonitrile, DMSO, DMF, methanol or an ethereal solvent, preferably THF, at a temperature range of about 0°C to about 70°C, for a period from about 4 hours to about 48 hours. Optionally such reactions can be performed in the presence of a perchlorate salt, such as lithium or magnesium perchlorate. Other similar methods are described in J. Org. Chem., 2514-2525 (1995).

[0120] The compound of the formula V, wherein Y is -O- and P is hydrogen or a protecting group, is prepared from 45 a compound of the formula VI by epoxidation using a suitable oxidant such as a peracid or peroxide based oxidant. One of ordinary skill in the art will appreciate that such oxidations can be facilitated by a transition metal catalyst and can be performed enantioselectively under so-called Sharpless or Jacobsen conditions. Either enantiomer of V may be prepared by oxidation in the presence of the appropriate enantiomer of the chiral ligand. In the case of the Sharpless epoxidation, this would be either (D) or (L) diisopropyl tartrate. For preparation of the racemic compounds, suitable 50 oxidants include tert-butylhydroperoxide. Suitable solvents include benzene or toluene in the presence of a metal catalyst, preferably a vanadium catalyst, most preferably vanadyl acetoacetone at a temperature range from ambient temperature to the boiling point of the solvent, for a period from about 1 hours to about 12 hours.

[0121] The compound of the formula V, wherein Y is >NR¹⁴ and R¹⁴ is alkyl-O-(C=O)- or -(SO₂)-alkyl and P is hydrogen, is prepared from a compound of the formula VI by reaction with an aziridination reagent such as alkyl-O-(C=O)- 55 NH-O-SO₂-aryl, aryl-SO₂-NH-Cl or alkyl-O-(C=O)-N₃, in the presence of a transition metal catalyst (such as a Cu(II) catalyst) or by photochemical irradiation. Suitable solvents include benzene or toluene. The aforesaid reaction may be performed at a temperature range from about about 10°C to about the boiling point of the solvent (e.g. 100°C), for a time sufficient for the full conversion (about 1 to about 12 hours). Similar methods are also described in Tetrahedron,

14105-14112 (1998).

[0122] A compound of the formula V, wherein Y is -O- or >NR¹⁴ and R¹⁴ is alkyl-(C=O)- or aryl(SO₂)- and P is a protecting group such as a silyl protecting group (such as *t*-butyl dimethyl silyl ether), may be prepared from a compound of the formula V, wherein Y is -O- or >NR¹⁴ and R¹⁴ is alkyl-(C=O)- or aryl(SO₂)- and P is hydrogen, by reaction with an activated protecting group such as *t*-butyl-dimethyl-silyl chloride or trimethylsilyl chloride in the presence of a base such as pyridine, 2,6-lutidine, imidazole or diisopropylethylamine, preferably triethylamine or imidazole. Suitable solvents include methylene chloride, DMF or toluene. The reaction is performed at a temperature of about 0° to about 22°C (i.e., room temperature) for about 1 to about 12 hours, preferably about 1 hour.

[0123] Compounds of formula VI are well known in the literature or are commercially available. Compounds of the formula VI can also be prepared according to the methods of Scheme 7.

[0124] Scheme 3 refers to the preparation of compounds of the formula II, wherein Z is -OR¹¹ or >NR¹²R¹³ and R¹¹ is other than hydrogen or at least one of R¹² and R¹³ is other than hydrogen. Said compounds of the formula II can be converted to compounds of formula I according to the methods of Scheme 1, for the conversion of compounds of the formula II to formula I.

[0125] Referring to Scheme 3, a compound compound of the formula II, wherein Z is -OR¹¹ or >NR¹²R¹³ and R¹¹ is other than hydrogen or at least one of R¹² and R¹³ is other than hydrogen, may be prepared from a compound of the formula VII, wherein Z is -OR¹¹ or >NR¹²R¹³ and R¹¹ is other than hydrogen or at least one of R¹² and R¹³ is other than hydrogen, by treatment with a suitable oxidant, such as Jones Reagent or under other known conditions employing an alkali metal chlorite salt, preferably sodium chlorite in the presence of a suitable catalyst, such as a mixture of 22,6,6-tetramethyl-1-piperidinyloxy free radical (TEMPO) and sodium hypochlorite in a pH 7 buffered aqueous solution, with an appropriate aprotic polar cosolvent, preferably acetonitrile, from about 0°C to about 50°C, for about four to about 12 hours.

[0126] The compound of the formula VII, wherein Z is -OR¹¹ or >NR¹²R¹³ and R¹¹ is other than hydrogen or at least one of R¹² and R¹³ is other than hydrogen, can be prepared from a compound of formula III, wherein Z is -OR¹¹ or >NR¹²R¹³ and R¹¹ is other than hydrogen or at least one of R¹² and R¹³ is other than hydrogen and P is a protecting group (such as *t*-butyldimethylsilyl), by reaction with a strong acid such as trifluoroacetic acid or by reaction with a fluoride source such as boron trifluoride etherate.

[0127] The compound of the formula III, wherein Z is -OR¹¹ or -NR¹²R¹³ and R¹¹ is other than hydrogen or at least one of R¹² and R¹³ is other than hydrogen and P is a protecting group, can be prepared from compounds of the formula III, from Scheme 1, wherein Z is -OR¹¹ or -NR¹²R¹³ and R¹¹, R¹² and R¹³ are each hydrogen and P is a protecting group, by reaction with an alkylating or acylating agent. When the reactant is an alkylating reagent, such as R¹¹-L, R¹²-L or R¹³-L and L is a halogen such as iodo, bromo or chloro, and Z is -OR¹¹ then the reaction is performed in the presence of a suitable base, such as sodium hydride, potassium hydride, sodium hexamethydisalicyzide, in a polar solvent such as tetrahydrofuran or dimethylformamide, at a temperature of about 0°C to about the reflux temperature of the solvent for a period from about 15 minutes to about 4 hours. When the reactant is an alkylating reagent, such as R¹¹-L, R¹²-L or R¹³-L and L is a halogen such as iodo, bromo or chloro, and Z is >NR¹²R¹³, then the presence of a base is optional (i.e. the nitrogen atom may serve as the molecule's own base). When the alkylating agent is an aldehyde or ketone (such as alkyl(C=O)-H or alkyl(C=O)alkyl) then the condensation is performed in the presence of a reducing reagent such as sodium cyano borohydride. When the reactant is an acylating reagent (e.g., alkyl(C=O)-L, wherein L is halo) then the reaction is performed in the presence of a suitable base, such as triethylamine or pyridine, in a polar solvent such as methylene chloride or THF, at a temperature of about 0°C to about 40°C for a period from about 15 minutes to about 4 hours.

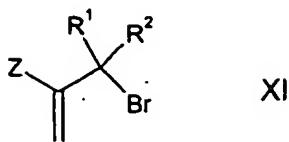
[0128] Scheme 4 refers to the preparation of compounds of the formula III, wherein Z is optionally substituted alkyl and P is hydrogen. Said compounds of the formula III can be converted to compounds of the formula I according to the methods of Scheme 1.

[0129] Referring to Scheme 4, a compound of the formula III, wherein Z is optionally substituted alkyl and P is hydrogen, can be prepared from a compound of the formula VIII by reaction with a suitable base in a polar aprotic solvent. Suitable bases include lithium dialkylamides (e.g. lithium diisopropylamide). Suitable solvents include tetrahydrofuran, diglyme or ether. The aforesaid reaction can be performed at a temperature of about -78°C to about 0°C for a period from about 15 minutes to about 4 hours.

[0130] A compound of formula VIII can be prepared by epoxidation of a compound of formula IX using a suitable oxidant such as a peracid or peroxide based oxidant. One of ordinary skill in the art will appreciate that such oxidations can be facilitated by a transition metal catalyst and can be performed enantioselectively under so-called Jacobsen conditions. The epoxide may be formed as the racemate by treating the compound of formula IX with a suitable oxidant, such as metachloroperbenzoic acid in a suitable solvent, such as methylene chloride ether or toluene at a temperature range from about 0°C to the boiling point of the solvent (100°C), for a time sufficient for the full conversion.

[0131] A compound of formula IX can be prepared from a compound of formula X by reaction with a compound of the formula

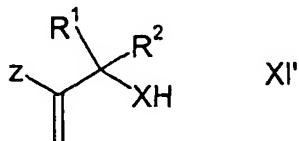
5



wherein Z is optionally substituted alkyl, in the presence of a suitable base and a suitable solvent. Suitable bases include sodium hydride or potassium hydride. Suitable solvents include tetrahydrofuran or DMF. The aforesaid reaction can be performed at a temperature of about about 0°C to about 80°C for a period from about 2 hours to about 24 hours. [0132] Alternatively, a compound of formula IX can be prepared from a compound of formula X', wherein the hydroxy group in the compound of formula X has been converted to a leaving group such as tosylate according to methods well known to those skilled in the art, by reaction with a compound of the formula

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wherein Z is optionally substituted alkyl, in the presence of a suitable base and a suitable solvent. Suitable bases include sodium hydride or potassium hydride. Suitable solvents include tetrahydrofuran or DMF. The aforesaid reaction can be performed at a temperature of about about 0°C to about 80°C for a period from about 2 hours to about 24 hours.

[0133] A compound of the formula X can be prepared from a compound of the formula XII by reaction with a hydride reagent such as lithium aluminum hydride, lithium triethyl borohydride or lithium borohydride, preferably lithium aluminum hydride, in an inert solvent solvent such as THF or ether, preferably THF, at a temperature of from about 0°C to about 25°C, preferably about 20°C to about room temperature for a period of time of from about 10 minutes to about 1 day, preferably about 1 hour.

[0134] A compound of formula XII, wherein n is 2, can be prepared from a compound of formula XII, wherein n is zero, by reaction with an oxidant such as m-CPBA or peracetic acid in an aprotic solvent such as methylene chloride at about 0°C to about 40°C for about 2 to about 24 hours.

[0135] A compound of the formula XII, wherein n is zero, can be prepared from a compound of the formula XIII by reaction with a compound of the formula QSH in the presence of a suitable base in a suitable solvent. Suitable bases include sodium hydride. Suitable solvents include tetrahydrofuran or DMF. The aforesaid reaction can be performed at a temperature of about about 0°C to about the reflux temperature of the solvent (e.g., 50°C for THF) for a period from about 2 hours to about 24 hours.

[0136] Compounds of the formula XIII are commercially available or can be made by methods well known to those skilled in the art.

[0137] Scheme 5 refers to an alternate preparation of compounds of the formula III, wherein Q is heterocyclic and the point of attachment of Q to the ring is through a heteroatom such as N.

[0138] Referring to Scheme 5, a compound of the formula III is prepared from a compound of formula XVII by reaction with a compound of the formula QH, wherein the H (i.e. hydrogen) is attached to a ring nitrogen atom in the presence of a base (such as pyridine or triethylamine), in a polar solvent such as methylene chloride DMF or THF. The temperature of the aforesaid reaction is from about 0°C to about 50°C, and the reaction is run for about 10 minutes to about 4 hours.

[0139] The compound of formula XVII is prepared from a compound of formula XVIII by reaction with a chlorinating agent. Suitable chlorinating agents includes POCl_3 , PCl_5 or SOCl_2 or mixtures of triphenylphosphine and hexachloroethane. The aforesaid reaction is run at a temperature of about 0°C to about 100°C for a period from about 1 hour to about 5 hours.

[0140] The compound of formula XVIII is prepared from a compound of formula V by reaction with sodium thiosulfate or sodium sulfite in a polar solvent. Suitable solvents include alcohols and water, preferably an ethanol water mixture such as 3:1 ethanol water. The reaction is run for about 5 hours to about 24 hours at a temperature from about 50°C to about 100°C.

[0141] The compounds of the formula V can be prepared according to the methods of Scheme 2.

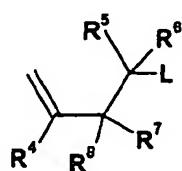
[0142] Scheme 6 refers to preparation of compounds of the formula XIV. Referring to Scheme 6, compounds of the formula XIV are prepared from a compound of the formula XV by reduction of the sulfonyl chloride using a suitable reducing agent, such as a metal reducing agent, preferably zinc, in an appropriate solvent, such as an acidic solvent, preferably acetic acid or mixtures of water and HCl at a temperature between 0°C and 80°C for a period of time sufficient

to convert XV to XIV. Compounds of the formula XV are commercially available or can be prepared by methods well known to those skilled in the art.

[0143] Scheme 7 refers to preparation of compounds of the formula VI, which are intermediates in Scheme 2.

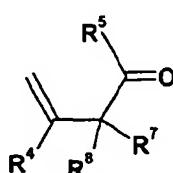
[0144] Referring to Scheme 7, compounds of the formula VI may be prepared under so-called Grubbs Metathesis 5 conditions by treating a compound of the formula XX with a ruthenium catalyst, preferably bis (tricyclohexylphosphine) benzylidene ruthenium (IV) dichloride in a suitable solvent such as methylene chloride or dichloroethane at a temperature between about 23°C and about 60°C for about 2 to about 12 hours.

[0145] Compounds of the formula XX can be prepared by alkylation of compounds of the formula XXI, wherein X is 10 O with a compound of the formula



XXIIa

20 wherein L is a leaving group, such as but-3-enyl-1-iodide, in the presence of a suitable base, such as sodium hydride or potassium hydride in a polar aprotic solvent, such as DMF or THF. In the case where X is N, similar conditions may be used. Alternatively the compound of formula XXI may be treated with the appropriate compound of formula XXIIb



XXIIb

35 such as 3-butenone, in the presence of a suitable reducing agent such as sodium cyanoborohydride in a polar solvent, preferably methanol.

[0146] Compounds of the formula XXI can be prepared by treating a compound of the formula XXIII with an alkyl 40 lithium, such as n-butyllithium or t-butyllithium in an ethereal solvent, preferably THF or ether at a temperature between -78°C to -50°C. The appropriately substituted ketone (such as R1R2(C=O)) or protected imine (such as R1R2(C=N)-benzyl) is then added and allowed to react at a temperature between about -78 °C and about 23 °C for about 2 to about 24 hours.

[0147] The ability of the compounds of formula I or their pharmaceutically acceptable salts (hereinafter also referred to as the compounds of the present invention) to inhibit metalloproteinases or mammalian reproxin and, consequently, 45 demonstrate their effectiveness for treating diseases characterized by metalloproteinase or mammalian reproxin disregulation (e.g., the over production of tumor necrosis factor or aggrecanase preferably aggrecanase) is shown by the following in vitro assay tests.

BIOLOGICAL ASSAYS

50 [0148] The ability of the compounds of formula I or their pharmaceutically acceptable salts (hereinafter also referred to as the compounds of the present invention) to inhibit metalloproteinases or mammalian reproxin and, consequently, demonstrate their effectiveness for treating diseases characterized by metalloproteinase or the mammalian reproxin activity (such as the inhibition of aggrecanase) is shown by the following in vitro assay tests.

MMP Assays

[0149] Collagenase-3 (matrix metalloproteinase-13) selective inhibitors as used herein refer to agents which exhibit

at least a 100 fold selectivity for the inhibition of collagenase-3 enzyme activity over collagenase-1 enzyme activity and a potency of less than 100 nM as defined by the IC₅₀ results from the MMP-13/MMP-1 fluorescence assays described below. Collagenase-3 selective inhibitors can be identified by screening the inhibitors of the present invention through the MMP-13/MMP-1 fluorescence assays described below and selecting those agents with MMP-13/MMP-1 inhibition IC₅₀ ratios of 100 or greater and potency of less than 100 nM.

[0150] Non-selective collagenase inhibitors as used herein refer to agents which exhibit less than a 100 fold selectivity for the inhibition of collagenase-3 enzyme activity and/or Aggrecanase activity over collagenase-1 enzyme activity or a potency of more than 10 μ M, more preferably 1 μ M, most preferably 100nM, as defined by the IC₅₀ results from the MMP-13 fluorescence assay and/or Aggrecanase *in vitro* assay described below.

[0151] The ability of collagenase inhibitors to inhibit collagenase activity is well known in the art. The following assays may be used to identify matrix metalloproteinase inhibitors.

Inhibition of Human Collagenase (MMP-1)

[0152] Human recombinant collagenase is activated with trypsin. The amount of trypsin is optimized for each lot of collagenase-1 but a typical reaction uses the following ratio: 5 μ g trypsin per 100 μ g of collagenase. The trypsin and collagenase are incubated at room temperature for 10 minutes then a five fold excess (50 mg/10 mg trypsin) of soybean trypsin inhibitor is added.

[0153] Stock solutions (10 mM) of inhibitors are made up in dimethylsulfoxide and then diluted using the following scheme:

10 mM ----> 120 μ M ----> 12 μ M ----> 1.2 μ M ----> 0.12 μ M

Twenty-five microliters of each concentration is then added in triplicate to appropriate wells of a 96 well microfluor plate. The final concentration of inhibitor will be a 1:4 dilution after addition of enzyme and substrate. Positive controls (enzyme, no inhibitor) are set up in wells D7-D12 and negative controls (no enzyme, no inhibitors) are set in wells D1-D6.

[0154] Collagenase-1 is diluted to 240 ng/ml and 25 μ l is then added to appropriate wells of the microfluor plate. Final concentration of collagenase in the assay is 60 ng/ml.

[0155] Substrate (DNP-Pro-Cha-Gly-Cys(Me)-His-Ala-Lys(NMA)-NH₂) is made as a 5 mM stock in dimethylsulfoxide and then diluted to 20 μ M in assay buffer. The assay is initiated by the addition of 50 μ l substrate per well of the microfluor plate to give a final concentration of 10 μ M.

[0156] Fluorescence readings (360 nM excitation, 460 nm emission) are taken at time 0 and then at 20 minute intervals. The assay is conducted at room temperature with a typical assay time of 3 hours

[0157] Fluorescence versus time is then plotted for both the blank and collagenase containing samples (data from triplicate determinations is averaged). A time point that provides a good signal (at least five fold over the blank) and that is on a linear part of the curve (usually around 120 minutes) is chosen to determine IC₅₀ values. The zero time is used as a blank for each compound at each concentration and these values are subtracted from the 120 minute data. Data is plotted as inhibitor concentration versus % control (inhibitor fluorescence divided by fluorescence of collagenase alone x 100). IC₅₀'s are determined from the concentration of inhibitor that gives a signal that is 50% of the control.

[0158] If IC₅₀'s are reported to be less than 0.03 μ M then the inhibitors are assayed at concentrations of 0.3 μ M, 0.03 μ M, and 0.003 μ M.

Inhibition of Gelatinase (MMP-2)

[0159] Human recombinant 72 kD gelatinase (MMP-2, gelatinase A) is activated for 16-18 hours with 1mM p-aminophenyl-mercuric acetate (from a freshly prepared 100 mM stock in 0.2 N NaOH) at 4°C, rocking gently.

[0160] 10 mM dimethylsulfoxide stock solutions of inhibitors are diluted serially in assay buffer (50 mM TRIS, pH 7.5, 200 mM NaCl, 5 mM CaCl₂, 20 μ M ZnCl₂ and 0.02% BRIJ-35 (vol./vol.)) using the following scheme:

10 mM--> 120 μ M--> 12 μ M--> 1.2 μ M--> 0.12 μ M

Further dilutions are made as necessary following this same scheme. A minimum of four inhibitor concentrations for each compound are performed in each assay. 25 μ L of each concentration is then added to triplicate wells of a black 96 well U-bottomed microfluor plate. As the final assay volume is 100 μ L, final concentrations of inhibitor are the result of a further 1:4 dilution (i.e. 30 μ M ----> 3 μ M ----> 0.3 μ M ----> 0.03 μ M, etc.). A blank (no enzyme, no inhibitor) and a positive enzyme control (with enzyme, no inhibitor) are also prepared in triplicate.

[0161] Activated enzyme is diluted to 100 ng/mL in assay buffer, 25 μ L per well is added to appropriate wells of the microplate. Final enzyme concentration in the assay is 25 ng/mL (0.34 nM).

[0162] A five mM dimethylsulfoxide stock solution of substrate (Mca-Pro-Leu-Gly-Leu-Dpa-Ala-Arg-NH₂) is diluted in assay buffer to 20 μ M. The assay is initiated by addition of 50 μ L of diluted substrate yielding a final assay concentration of 10 μ M substrate. At time zero, fluorescence reading (320 excitation; 390 emission) is immediately taken and subsequent readings are taken every fifteen minutes at room temperature with a PerSeptive Biosystems CytoFluor Multi-Well Plate Reader with the gain at 90 units.

[0163] The average value of fluorescence of the enzyme and blank are plotted versus time. An early time point on the linear part of this curve is chosen for IC₅₀ determinations. The zero time point for each compound at each dilution is subtracted from the latter time point and the data then expressed as percent of enzyme control (inhibitor fluorescence divided by fluorescence of positive enzyme control x 100). Data is plotted as inhibitor concentration versus percent of enzyme control. IC₅₀'s are defined as the concentration of inhibitor that gives a signal that is 50% of the positive enzyme control.

15 Inhibition of Stromelysin Activity (MMP-3)

[0164] Human recombinant stromelysin (MMP-3, stromelysin-1) is activated for 20-22 hours with 2 mM p-aminophenyl-mercuric acetate (from a freshly prepared 100 mM stock in 0.2 N NaOH) at 37°C.

[0165] 10 mM dimethylsulfoxide stock solutions of inhibitors are diluted serially in assay buffer (50 mM TRIS, pH 7.5, 20 mM NaCl, 10 mM CaCl₂ and 0.05% BRIJ-35 (vol./vol.)) using the following scheme:

10 mM \rightarrow 120 μ M \rightarrow 12 μ M \rightarrow 1.2 μ M \rightarrow 0.12 μ M

25 Further dilutions are made as necessary following this same scheme. A minimum of four inhibitor concentrations for each compound are performed in each assay. 25 μ L of each concentration is then added to triplicate wells of a black 96 well U-bottomed microfluor plate. As the final assay volume is 100 μ L, final concentrations of inhibitor are the result of a further 1:4 dilution (i.e. 30 μ M \rightarrow 3 μ M \rightarrow 0.3 μ M \rightarrow 0.03 μ M, etc.). A blank (no enzyme, no inhibitor) and a positive enzyme control (with enzyme, no inhibitor) are also prepared in triplicate.

30 [0166] Activated enzyme is diluted to 200 ng/mL in assay buffer, 25 μ L per well is added to appropriate wells of the microplate. Final enzyme concentration in the assay is 50 ng/mL (0.875 nM).

[0167] A ten mM dimethylsulfoxide stock solution of substrate (Mca-Arg-Pro-Lys-Pro-Val-Glu-Nva-Trp-Arg-Lys(Dnp)-NH₂) is diluted in assay buffer to 6 μ M. The assay is initiated by addition of 50 μ L of diluted substrate yielding a final assay concentration of 3 μ M substrate. At time zero, fluorescence reading (320 excitation; 390 emission) is immediately taken and subsequent readings are taken every fifteen minutes at room temperature with a PerSeptive Biosystems CytoFluor Multi-Well Plate Reader with the gain at 90 units.

[0168] The average value of fluorescence of the enzyme and blank are plotted versus time. An early time point on the linear part of this curve is chosen for IC₅₀ determinations. The zero time point for each compound at each dilution is subtracted from the latter time point and the data then expressed as percent of enzyme control (inhibitor fluorescence divided by fluorescence of positive enzyme control x 100). Data is plotted as inhibitor concentration versus percent of enzyme control. IC₅₀'s are defined as the concentration of inhibitor that gives a signal that is 50% of the positive enzyme control.

Inhibition of Human 92 kD Gelatinase (MMP-9)

[0169] Inhibition of 92 kD gelatinase (MMP-9) activity is assayed using the Mca-Pro-Leu-Gly-Leu-Dpa-Ala-Arg-NH₂ substrate (10 μ M) under similar conditions as described above for the inhibition of human collagenase (MMP-1).

[0170] Human recombinant 92 kD gelatinase (MMP-9, gelatinase B) is activated for 2 hours with 1mM p-aminophenyl-mercuric acetate (from a freshly prepared 100 mM stock in 0.2 N NaOH) at 37 C.

50 [0171] 10 mM dimethylsulfoxide stock solutions of inhibitors are diluted serially in assay buffer (50 mM TRIS, pH 7.5, 200 mM NaCl, 5 mM CaCl₂, 20 μ M ZnCl₂, 0.02% BRIJ-35 (vol./vol.)) using the following scheme:

10 mM \rightarrow 120 μ M \rightarrow 12 μ M \rightarrow 1.2 μ M \rightarrow 0.12 μ M

55 [0172] Further dilutions are made as necessary following this same scheme. A minimum of four inhibitor concentrations for each compound are performed in each assay. 25 μ L of each concentration is then added to triplicate wells of a black 96 well U-bottomed microfluor plate. As the final assay volume is 100 μ L, final concentrations of inhibitor are

the result of a further 1:4 dilution (i.e. 30 μ M \rightarrow 3 μ M \rightarrow 0.3 μ M \rightarrow 0.03 μ M, etc.). A blank (no enzyme, no inhibitor) and a positive enzyme control (with enzyme, no inhibitor) are also prepared in triplicate.

[0173] Activated enzyme is diluted to 100 ng/mL in assay buffer, 25 μ L per well is added to appropriate wells of the microplate. Final enzyme concentration in the assay is 25 ng/mL (0.27 nM).

5 [0174] A five mM dimethylsulfoxide stock solution of substrate (Mca-Pro-Leu-Gly-Leu-Dpa-Ala-Arg-NH₂) is diluted in assay buffer to 20 μ M. The assay is initiated by addition of 50 μ L of diluted substrate yielding a final assay concentration of 10 μ M substrate. A 0 time fluorescence reading (320 excitation; 390 emission) is immediately taken and subsequent readings are taken every fifteen minutes at room temperature with a PerSeptive Biosystems CytoFluor Multi-Well Plate Reader with the gain at 90 units.

10 [0175] The average value of fluorescence of the enzyme and blank are plotted versus time. An early time point on the linear part of this curve is chosen for IC₅₀ determinations. The 0 time point for each compound at each dilution is subtracted from the latter time point and the data then expressed as percent of enzyme control (inhibitor fluorescence divided by fluorescence of positive enzyme control \times 100). Data is plotted as inhibitor concentration versus percent of enzyme control. IC₅₀'s are defined as the concentration of inhibitor that gives a signal that is 50% of the positive enzyme

15 control.

Inhibition of MMP-13

20 [0176] Human recombinant MMP-13 is activated with 2 mM APMA (p-aminophenyl mercuric acetate) for 1.5 hours, at 37°C and is diluted to 400 mg/ml in assay buffer (50 mM Tris, pH 7.5, 200 mM sodium chloride, 5 mM calcium chloride, 20 μ M zinc chloride, 0.02% brij). Twenty-five microliters of diluted enzyme is added per well of a 96 well microfluor plate. The enzyme is then diluted in a 1:4 ratio in the assay by the addition of inhibitor and substrate to give a final concentration in the assay of 100 mg/ml.

25 [0177] 10 mM stock solutions of inhibitors are made up in dimethyl sulfoxide and then diluted in assay buffer as per the inhibitor dilution scheme for inhibition of human collagenase (MMP-1): Twenty-five microliters of each concentration is added in triplicate to the microfluor plate. The final concentrations in the assay are 30 μ M, 3 μ M, 0.3 μ M, and 0.03 μ M.

30 [0178] Substrate (Dnp-Pro-Cha-Gly-Cys(Me)-His-Ala-Lys(NMA)-NH₂) is prepared as for inhibition of human collagenase (MMP-1) and 50 μ L is added to each well to give a final assay concentration of 10 μ M. Fluorescence readings (360 nM excitation; 450 emission) are taken at time 0 and every 5 minutes for 1 hour.

[0179] Positive controls consist of enzyme and substrate with no inhibitor and blanks consist of substrate only.

[0180] IC₅₀'s are determined as per inhibition of human collagenase (MMP-1). If IC₅₀'s are reported to be less than 0.03 μ M, inhibitors are then assayed at final concentrations of 0.3 μ M, 0.03 μ M, 0.003 μ M and 0.0003 μ M.

Collagen film MMP-13 Assay

35 [0181] Rat type I collagen is radiolabeled with ¹⁴C acetic anhydride (T.E. Cawston and A.J. Barrett, *Anal. Biochem.*, 99, 340-345 (1979)) and used to prepare 96 well plates containing radiolabeled collagen films (Barbara Johnson-Wint, *Anal. Biochem.*, 104, 175-181 (1980)). When a solution containing collagenase is added to the well, the enzyme cleaves the insoluble collagen which unwinds and is thus solubilized. Collagenase activity is directly proportional to the amount 40 of collagen solubilized, determined by the proportion of radioactivity released into the supernatant as measured in a standard scintillation counter. Collagenase inhibitors are, therefore, compounds which reduce the radioactive counts released with respect to the controls with no inhibitor present. One specific embodiment of this assay is described in detail below.

45 [0182] For determining the selectivity of compounds for MMP-13 versus MMP-1 using collagen as a substrate, the following procedure is used. Recombinant human proMMP-13 or proMMP-1 is activated according to the procedures outlined above. The activated MMP-13 or MMP-1 is diluted to 0.6 μ g/ml with buffer (50 mM Tris pH 7.5, 150 mM NaCl, 10 mM CaCl₂, 1 μ M ZnCl₂, 0.05% Brij-35, 0.02% sodium azide).

50 [0183] Stock solutions of test compound (10mM) in dimethylsulfoxide are prepared. Dilutions of the test compounds in the Tris buffer, above, are made to 0.2, 2.0, 20, 200, 2000 and 20000 nM.

[0184] 100 μ L of appropriate drug dilution and 100 μ L of diluted enzyme are pipetted into wells of a 96 well plate containing collagen films labeled with ¹⁴C-collagen. The final enzyme concentration is 0.3 μ g/ml while the final drug concentration is 0.1, 1.0, 10, 100, 1000 nM. Each drug concentration and control is analyzed in triplicate. Triplicate controls are also run for the conditions in which no enzyme is present and for enzyme in the absence of any compound.

55 [0185] The plates are incubated at 37°C for a time period such that around 30 - 50% of the available collagen is solubilized - determined by counting additional control wells at various time points. In most cases around 9 hours of incubation are required. When the assay has progressed sufficiently, the supernatant from each well is removed and counted in a scintillation counter. The background counts (determined by the counts in the wells with no enzyme) are subtracted from each sample and the % release calculated in relation to the wells with enzyme only and no inhibitor.

The triplicate values for each point are averaged and the data graphed as percent release versus drug concentration. IC₅₀'s are determined from the point at which 50% inhibition of release of radiolabeled collagen is obtained.

[0186] To determine the identity of the active collagenases in cartilage conditioned medium, assays were carried out using collagen as a substrate, cartilage conditioned medium containing collagenase activity and inhibitors of varying 5 selectivity. The cartilage conditioned medium was collected during the time at which collagen degradation was occurring and thus is representative of the collagenases responsible for the collagen breakdown. Assays were carried out as outlined above except that instead of using recombinant MMP-13 or recombinant MMP-1, cartilage conditioned medium was the enzyme source.

10 **IL-1 Induced Cartilage Collagen Degradation From Bovine Nasal Cartilage**

[0187] This assay uses bovine nasal cartilage explants which are commonly used to test the efficacy of various compounds to inhibit either IL-1 induced proteoglycan degradation or IL-1 induced collagen degradation. Bovine nasal cartilage is a tissue that is very similar to articular cartilage, i.e. chondrocytes surrounded by a matrix that is primarily 15 type II collagen and aggrecan. The tissue is used because it: (1) is very similar to articular cartilage, (2) is readily available, (3) is relatively homogeneous, and (4) degrades with predictable kinetics after IL-1 stimulation.

[0188] Two variations of this assay have been used to assay compounds. Both variations give similar data. The two variations are described below:

20 **Variation 1**

[0189] Three plugs of bovine nasal cartilage (approximately 2 mm diameter x 1.5 mm long) are placed into each well of a 24 well tissue culture plate. One ml of serumless medium is then added to each well. Compounds are prepared as 10 mM stock solutions in DMSO and then diluted appropriately in serumless medium to final concentrations, e.g., 25 50, 500 and 5000 nM. Each concentration is assayed in triplicate.

[0190] Human recombinant IL-1 α (5ng/mL) (IL-1) is added to triplicate control wells and to each well containing drug. Triplicate control wells are also set up in which neither drug nor IL-1 are added. The medium is removed and fresh 30 medium containing IL-1 and the appropriate drug concentrations is added on days 6, 12, 18 and 24 or every 3 - 4 days if necessary. The media removed at each time point is stored at -20°C for later analysis. When the cartilage in the IL-1 alone wells has almost completely resorbed (about day 21), the experiment is terminated. The medium is removed and stored. Aliquots (100 μ l) from each well at each time point are pooled, digested with papain and then analyzed for hydroxyproline content. Background hydroxyproline (average of wells with no IL-1 and no drug) is subtracted from each data point and the average calculated for each triplicate. The data is then expressed as a percent of the IL-1 alone average value and plotted. The IC₅₀ is determined from this plot.

35

Variation 2

[0191] The experimental set-up is the same as outlined above in Variation 1, until day 12. On day 12, the conditioned 40 medium from each well is removed and frozen. Then one ml of phosphate buffered saline (PBS) containing 0.5 μ g/ml trypsin is added to each well and incubation continued for a further 48 hours at 37°C. After 48 hours incubation in trypsin, the PBS solution is removed. Aliquots (50 μ l) of the PBS/trypsin solution and the previous two time points (days 6 and 12) are pooled, hydrolyzed and hydroxyproline content determined. Background hydroxyproline (average of wells with no IL-1 and no drug) is subtracted from each data point and the average calculated for each triplicate. The data is then expressed as a percent of the IL-1 alone average value and plotted. The IC₅₀ is determined from this plot. 45 In this variation, the time course of the experiment is shortened considerably. The addition of trypsin for 48 hours after 12 days of IL-1 stimulation likely releases any type II collagen that has been damaged by collagenase activity but not yet released from the cartilage matrix. In the absence of IL-1 stimulation, trypsin treatment produces only low background levels of collagen degradation in the cartilage explants.

50 **Inhibition of TNF Production**

[0192] The ability of the compounds or the pharmaceutically acceptable salts thereof to inhibit the production of TNF and, consequently, demonstrate their effectiveness for treating diseases involving the production of TNF is shown by the following in vitro assay:

55

Human Monocyte Assay

[0193] Human mononuclear cells were isolated from anti-coagulated human blood using a one-step Ficoll-hypaque

separation technique. (2) The mononuclear cells were washed three times in Hanks balanced salt solution (HBSS) with divalent cations and resuspended to a density of 2×10^6 /ml in HBSS containing 1% BSA. Differential counts determined using the Abbott Cell Dyn 3500 analyzer indicated that monocytes ranged from 17 to 24% of the total cells in these preparations.

5 [0194] 180 μ l of the cell suspension was aliquoted into flat bottom 96 well plates (Costar). Additions of compounds and LPS (100 ng/ml final concentration) gave a final volume of 200 μ l. All conditions were performed in triplicate. After a four hour incubation at 37°C in an humidified CO₂ incubator, plates were removed and centrifuged (10 minutes at approximately 250 x g) and the supernatants removed and assayed for TNFa using the R&D ELISA Kit.

10 **Aggrecanase Assay**

[0195] Primary porcine chondrocytes from articular joint cartilage are isolated by sequential trypsin and collagenase digestion followed by collagenase digestion overnight and are plated at 2×10^5 cells per well into 48 well plates with 5 μ Ci /ml ³⁵S (1000 Ci/mmol) sulphur in type I collagen coated plates. Cells are allowed to incorporate label into their proteoglycan matrix (approximately 1 week) at 37°C, under an atmosphere of 5% CO₂.
 15 [0196] The night before initiating the assay, chondrocyte monolayers are washed two times in DMEM/ 1% PSF/G and then allowed to incubate in fresh DMEM /1% FBS overnight.
 [0197] The following morning chondrocytes are washed once in DMEM/1%PSF/G. The final wash is allowed to sit on the plates in the incubator while making dilutions.
 20 [0198] Media and dilutions can be made as described in the Table below.

| | |
|-------------------|---|
| Control Media | DMEM alone (control media) |
| IL-1 Media | DMEM + IL-1 (5 ng/ml) |
| 25 Drug Dilutions | Make all compounds stocks at 10 mM in DMSO. Make a 100 μ M stock of each compound in DMEM in 96 well plate. Store in freezer overnight. The next day perform serial dilutions in DMEM with IL-1 to 5 μ M, 500 nM, and 50 nM. 30 Aspirate final wash from wells and add 50 μ l of compound from above dilutions to 450 μ l of IL-1 media in appropriate wells of the 48 well plates. Final compound concentrations equal 500 nM, 50 nM, and 5 nM. All samples completed in triplicate with Control and IL-1 alone samples on each plate. |

35 [0199] Plates are labeled and only the interior 24 wells of the plate are used. On one of the plates, several columns are designated as IL-1 (no drug) and Control (no IL-1, no drug). These control columns are periodically counted to monitor 35S-proteoglycan release. Control and IL-1 media are added to wells (450 μ l) followed by compound (50 μ l) so as to initiate the assay. Plates are incubated at 37°C, with a 5% CO₂ atmosphere.
 40 [0200] At 40-50 % release (when CPM from IL-1 media is 4-5 times control media) as assessed by liquid scintillation counting (LSC) of media samples, the assay is terminated (9-12 hours). Media is removed from all wells and placed in scintillation tubes. Scintillate is added and radioactive counts are acquired (LSC). To solubilize cell layers, 500 μ l of papain digestion buffer (0.2 M Tris, pH 7.0, 5 mM EDTA, 5 mM DTT, and 1 mg/ml papain) is added to each well. Plates with digestion solution are incubated at 60°C overnight. The cell layer is removed from the plates the next day and placed in scintillation tubes. Scintillate is then added, and samples counted (LSC).
 45 [0201] The percent of released counts from the total present in each well is determined. Averages of the triplicates are made with control background subtracted from each well. The percent of compound inhibition is based on IL-1 samples as 0% inhibition (100% of total counts).

50 **IN VIVO ASSAYS**

[0202] Female golden Syrian hamsters (*Mesocricetus auratus*) strain LAK.LVG(SYR) can be purchased from Charles River Laboratories (Kingston, NY) at 100-110 g weight. They can be maintained on a 10/14 hr light/dark cycle with food and water ad libitum and acclimatized for approximately one week in standard housing before studies are initiated.
 55 [0203] For induction of arthritis, groups of 6 hamsters are anesthetized with sodium pentobarbital (80-100 mg/kg i. p.). Knees are cleaned and injected intraarticularly with an arthritogen (40 ng of IL-1 α or 2 μ g activated MMP-1 in 20 μ l of normal saline) through the patellar tendon into each knee joint using a 50 μ l syringe fitted with a 30 gauge needle. Oral administration of a compound of formula I is performed either after a certain period (e.g., 3 hours IL-1) or is predosed (e.g., 2 hours before MMP-13 arthritogen injection). A control group was untreated. After an additional three hours, the

hamsters are sacrificed with a sodium pentobarbital overdose and the synovial fluid lavaged. After surgically exposing the articular joint, three washes of 15 μ l of saline are used to lavage the synovial fluid. The lavage fluid from both knees is pooled for each animal in a 500 μ l conical tube and placed on ice. After centrifuging at 500xG to remove cells and debris, the samples can be frozen until assayed.

5 [0204] For IL-1, proteoglycan and hyaluronan can be determined on a 50 μ l aliquot of the papain-digested synovial fluid. An aliquot is transferred to a 0.5 ml polypropylene microcentrifuge tube, and 200 μ l of 50 mM phosphate buffer at pH 6.5, containing 1 mM EDTA, added. The sample is passed through a 30 x 0.78 cm TSK-GEL G5000PWXL column (TosoHass, Montgomeryville, PA) and the column effluent monitored at 206 nm. The first high molecular weight peak is hyaluronan. The sample is mixed post column with a solution containing 16 mg DMMB, 3.04 gm glycine, 2.37 gm sodium chloride, and 1.58 ml 6N HCl in 1 liter, and the amount of aggrecan read at 540 nm. Chondroitin sulfate is used as a standard for quantitation of aggrecan. The amount of aggrecan in a sample is expressed as μ g/ml of chondroitin sulfate standard.

10 [0205] To determine the effect of a drug on aggrecanase induced inflammation, the average concentration of aggrecan in the drug treated group was compared to the amount of aggrecan in the untreated group and a percentage inhibition calculated for each drug.

15 [0206] For MMP-13 an aliquot of synovial fluid is assayed by ELISA using an antibody to the neoepitope such as described in United States Patent 6,030,792.

20 [0207] For determination of TACE inhibition, 15 rats are separated into 3 groups. Each rat is dosed with drug or vehicle. Sixty minutes later, each rat is anesthetized with halothane and injected with 0.05 ml of 200 ug/ml PG-PS (Lee Laboratories product lot#126633) using a 1 cc syringe with a 30 g needle into the synovial cavity of both knees. Ninety minutes later, the rats are sacrificed. Each knee joint is exposed by surgery and lavaged with 0.3 ml lavage solution in 0.1 ml aliquots. The lavage solution is suctioned off the joint with glass disposable pipettes. The lavage is put in separate labeled 0.3 ml microfuge tubes and put on ice. The tubes are spun at 6000 rpm for 10 minutes in an Eppendorf centrifuge 5402. A portion of the supernatant (200 μ l) was pipetted off and put into fresh, labeled tubes and frozen at

25 -20°C until assayed for TNF α levels using an ELISA test.

25 [0208] The compounds of the present invention that were tested all have IC₅₀'s in at least one of the above assays of less than 100 μ M preferably less than 100nM. Certain preferred groups of compounds possess differential selectivity toward the various MMP's or ADAMs. One group of preferred compounds possess selective activity towards MMP-13 over MMP-1. Another preferred group of compounds possess selective aggrecanase activity over MMP-1. Another preferred group of compounds possess selective aggrecanase and MMP-13 activity over MMP-1. Another preferred group of compounds possess selective aggrecanase and MMP-13 activity over MMP-1 and TACE.

30 [0209] For administration to mammals, including humans, for the inhibition of matrix metalloproteinases or mammalian reprotoxin (preferably inhibition of Aggrecanase), a variety of conventional routes may be used including orally, parenterally and topically. In general, the active compound will be administered orally or parenterally at dosages between about 0.1 and 25 mg/kg body weight of the subject to be treated per day, preferably from about 0.3 to 5 mg/kg. However, some variation in dosage will necessarily occur depending on the condition of the subject being treated. The person responsible for administration will, in any event, determine the appropriate dose for the individual subject.

35 [0210] The compounds of the present invention can be administered in a wide variety of different dosage forms, in general, the therapeutically effective compounds of this invention are present in such dosage forms at concentration levels ranging from about 5.0% to about 70% by weight.

40 [0211] For oral administration, tablets containing various excipients such as microcrystalline cellulose, sodium citrate, calcium carbonate, dicalcium phosphate and glycine may be employed along with various disintegrants such as starch (and preferably corn, potato or tapioca starch), alginic acid and certain complex silicates, together with granulation binders like polyvinylpyrrolidone, sucrose, gelation and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often very useful for tabletting purposes. Solid compositions of a similar type may also be employed as fillers in gelatin capsules; preferred materials in this connection also include lactose or milk sugar as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral administration, the active ingredient may be combined with various sweetening or flavoring agents, coloring matter or dyes, and, if so desired, emulsifying and/or suspending agents as well, together with such diluents as water, ethanol, propylene glycol, glycerin and various like combinations thereof.

45 [0212] For parenteral administration (intramuscular, intraperitoneal, subcutaneous and intravenous use) a sterile injectable solution of the active ingredient is usually prepared. Solutions of a therapeutic compound of the present invention in either sesame or peanut oil or in aqueous propylene glycol may be employed. The aqueous solutions should be suitably adjusted and buffered, preferably at a pH of greater than 8, if necessary and the liquid diluent first rendered isotonic. These aqueous solutions are suitable intravenous injection purposes. The oily solutions are suitable for intraarticular, intramuscular and subcutaneous injection purposes. The preparation of all these solutions under sterile conditions is readily accomplished by standard pharmaceutical techniques well known to those skilled in the art.

50 [0213] The following Examples illustrate the preparation of the compounds of the present invention. Melting points

are uncorrected. NMR data are reported in parts per million (δ) and are referenced to the deuterium lock signal from the sample solvent (deuteriodimethylsulfoxide unless otherwise specified). Commercial reagents were utilized without further purification. THF refers to tetrahydrofuran. DMF refers to N,N-dimethylformamide. Chromatography refers to column chromatography performed using 32-63 mm silica gel and executed under nitrogen pressure (flash chromatography) conditions. Room or ambient temperature refers to 20-25°C. All non-aqueous reactions were run under a nitrogen atmosphere for convenience and to maximize yields. Concentration at reduced pressure means that a rotary evaporator was used.

EXAMPLE 1

4-[4-(2-CHLORO-BENZYLOXY)-BENZENESULFONYL]-3-HYDROXY-TETRAHYDRO-PYRAN-3-CARBOXYLIC ACID HYDROXYAMIDE

Step 1: 4-Benzylxy-benzenethiol

[0214] Zinc dust (13.1g) was added to a mixture of 4-Benzylxy-benzenesulfonyl chloride (I) (10g, 35.2mmoles), sulfuric acid (26.2g) and ice (78.6g) at 0°C. The mixture was warmed to ambient temperature, stirred for 1 hour, refluxed for 2 hours and then cooled to ambient temperature. The mixture was extracted twice with ethyl acetate and the combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo* to yield the title compound. ^1H NMR (CDCl_3 , 400MHz) δ 5.03 (s, 2H), 6.89 (d, J = 8.92 Hz, 2H), 7.38 (d, J = 8.93 Hz, 2H), 7.3-7.4 (m, 5H).

Step 2: (3,7-Dioxa-bicyclo[4.1.0]hept-1-yl)-methanol

[0215] Tert-butyl hydroperoxide (5.5M, 4.73 mmoles) was added to a mixture of vanadyl acetoacetone (0.058g, 0.22 mmoles) and hydroxymethylidihydro-pyran (0.5 g, 4.38 mmoles) in 16.2 ml of toluene at 85°C. After stirring for 5 minutes, TLC showed the reaction to be complete. The mixture was diluted with ethyl acetate and washed with 1 M hydrochloric acid followed by a wash with a saturated sodium bicarbonate solution. The ethyl acetate layer was dried over sodium sulfate, filtered and concentrated *in vacuo* to yield a light yellow oil (0.4g, 70%). ^1H NMR (D_6 acetone, 400MHz) δ 3.21 (bs, 1H), 3.36-3.42 (m, 2H), 3.48 (dd, J = 6.64 Hz and 12.04 Hz, 1H), 3.6 (dd, J = 5.61 Hz and 12.04 Hz, 1H), 3.74 (d, J = 13.07 Hz, 1H), 3.87 (dd, J = 5.6 Hz and 6.64 Hz, 1H), 4.02 (d, J = 13.07 Hz, 1H).

Step 3: 4-(4-Benzylxy-phenylsulfonyl)-3-hydroxymethyl-tetrahydro-pyran-3-ol

[0216] A mixture of benzylxy benzenethiol (1.5 g, 11.5 mmoles) and 30ml of THF at 0°C was treated with sodium hydride (0.48 g, 11.9 mmoles). After stirring for 20 minutes, an additional 20 ml of THF was added to reduce viscosity. The mixture was then treated with the product from Step 2, above, (5.01g, 23 mmoles), and was stirred for 2 hours at ambient temperature. The mixture was diluted with saturated ammonium chloride solution, and extracted three times with ethyl acetate. The organic layers were combined, dried with sodium sulfate, filtered and concentrated *in vacuo*. The residue was filtered through a pad of silica elute with 20% ethyl acetate in hexanes to remove the undesirable material, followed by ethyl acetate to elute the desired product. Concentration *in vacuo* yielded a colorless solid (2.6g, 65%). ^1H NMR (CDCl_3 , 400MHz) δ 1.70-1.79 (m, 1H), 2.0-2.08 (m, 1H), 2.2 (bs, 2H), 3.21 (dd, J = 4.57 Hz and 9.14 Hz, 1H), 3.27 (d, J = 11.63 Hz, 1H), 3.46-3.52 (m, 1H), 3.8 (dd, J = 11.63 Hz and 15.79 Hz, 2H), 3.87-3.94 (m, 2H), 5.04 (s, 2H), 6.91 (d, J = 9.14 Hz, 1H), 7.31-7.42 (m, 7H).

Step 4: 4-(4-Benzylxy-benzenesulfonyl)-3-hydroxymethyl-tetrahydro-pyran-3-ol

[0217] Peracetic acid (5.8g, 24.27mmoles) was added to a mixture of the product from the previous step (2.8g, 8.09 mmoles) and sodium acetate (5.7g, 70 mmoles) in 42 ml of methylene chloride at ambient temperature. (Caution: exothermic reaction). After stirring for 2 hours, the mixture was diluted with water and saturated sodium bicarbonate solution, then extracted with three portions of ethyl acetate. The combined organic layers were combined, dried with sodium sulfate, filtered and concentrated *in vacuo* to yield the title compound (2.5g, 85%). ^1H NMR (CDCl_3 , 400MHz) δ 1.61 (bd, 1H), 1.97-2.08 (m, 2H), 3.03 (d, J = 11.41 Hz, 1H), 3.27-3.36 (m, 2H), 3.90 (d, J = 12.24 Hz, 1H), 4.02 (dd, J = 4.89 Hz and 11.21 Hz, 1H), 4.06 (d, J = 11.41 Hz, 1H), 4.32 (d, J = 12.24 Hz, 1H), 7.10 (d, J = 8.93 Hz, 1H), 7.3-7.44 (m, 5H), 7.81 (d, J = 8.92 Hz, 1H).

Step 5: 4-(4-Hydroxy-benzenesulfonyl)-3-hydroxymethyl-tetrahydro-pyran-3-ol

[0218] A mixture of the product from the previous step (0.2g, 0.53 mmoles) dissolved in 10 ml of methyl alcohol

charged with 50 mg of palladium hydroxide on carbon, was shaken under a hydrogen atmosphere at 50 psi for 18 hours. The mixture was filtered through Celite® and concentrated *in vacuo* to yield the title compound (0.15g, 98%).

5 [0219] Step 5: HNMR (CD₃OD) δ 1.76-1.77 (m, 1H), 1.94-2.04 (m, 1H), 2.94 (d, J = 11.20 Hz, 1H), 3.40 (dd, J = 2.80 Hz and 11.51 Hz, 1H), 3.50 (dd, J = 4.36 Hz and 12.13 Hz, 1H), 3.97 (d, J = 11.85 Hz, 1H), 3.98-4.02 (m, 1H), 4.13 (d, J = 11.20 Hz, 1H), 4.19 (d, J = 12.13 Hz, 1H), 6.99 (d, J = 9.02 Hz, 2H), 7.77 (d, J = 8.71 Hz, 2H).

Step 6: 4-[4-(2-Chloro-benzyloxy)-benzenesulfonyl]-3-hydroxy-tetrahydro-pyran-3-carboxylic acid

10 [0220] To a mixture of the product from the previous step (115mg, 0.4 mmoles) and cesium carbonate (260 mg, 0.8 mmoles) in 1 ml DMF at ambient temperature was added 2-chlorobenzyl bromide (98 mg, 0.48 mmoles). After stirring for 18 hours the mixture was diluted with 1 M hydrochloric acid and extracted with ethyl acetate. The organic layer was dried with sodium sulfate, filtered and concentrated *in vacuo*. The residue was dissolved in 2 ml of acetonitrile and 1.5 ml of pH 7 phosphate buffer then added at ambient temperature in the following order, sodium chlorite 80% (0.8 mmoles), TEMPO (4 mg, 0.03 mmoles), and sodium hypochlorite 4% solution (0.22 ml, 0.1 mmoles). The reaction mixture was heated to 35°C for 3 hours, then removed heat and stirred an additional 18 hours. The reaction mixture was then quenched with 1N sodium hydroxide and some solid sodium sulfite. The mixture was poured into ether and extracted twice with 1N sodium hydroxide. The combined aqueous layers were acidified with 6N hydrochloric acid and then extracted 3 times with ethyl acetate. The ethyl acetate layers were combined, dried with sodium sulfate, filtered and concentrated *in vacuo* to yield the title compound (165mg, 97%).

15 [0221] Step 6: HMNR (CD₃OD) δ 2.01-2.03 (m, 1H), 2.43-2.61 (m, 1H), 3.21 (d, J = 11.51 Hz, 1H), 3.41-3.56 (m, 1H), 3.63 (dd, J = 4.98 Hz and 12.75 Hz, 1H), 3.83 (d, J = 11.82 Hz, 1H), 4.08-4.13 (m, 1H), 5.30 (s, 2H), 7.21 (d, J = 9.02 Hz, 2H), 7.35-7.38 (m, 2H), 7.47-7.51 (m, 1H), 7.57-7.60 (m, 1H), 7.88 (d, J = 9.02 Hz, 2H).

Step 7: 4-[4-(2-Chloro-benzyloxy)-benzenesulfonyl]-3-hydroxy-tetrahydro-pyran-3-carboxylic acid hydroxyamide

20 [0222] To a mixture of the product from the previous step (160 mg, 0.4 mmoles), 1-hydroxybenzotriazole hydrate (76 mg, 0.6 mmoles), allyl hydroxylamine hydrochloride (62 mg, 0.6 mmoles), diisopropylethylamine (0.13 ml, 0.7 mmoles) in 2 ml of anhydrous methylene chloride at room temperature, was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDCI). After stirring for 48 hours, the mixture was diluted with ethyl acetate, washed with 1M hydrochloric acid, sodium bicarbonate solution and brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residue was dissolved in 4 ml of 20% water in acetonitrile and was treated with 1.6 g of 5:2 (v/v) formic acid-triethylamine and 44 mg of tetrakis(triphenylphosphine)palladium(0) (Pd(PPh₃)₄). After being shaken at 85°C for 30 minutes, the mixture was diluted with ether and extracted 4 times into 1M sodium hydroxide. The combined aqueous layers were washed 3 times with ether, acidified to pH 1 with 6M hydrochloric acid and were extracted 3 times into ethyl acetate. The combined ethyl acetate extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The compound was purified by preparative TLC plate eluting with 10% methanol in methylene chloride. The silica was washed with 20% methanol in methylene chloride with 1% acetic acid, the filtrate concentrated *in vacuo*. After trituration and collection with isopropyl ether the product was isolated as a colorless solid (30mg, 18%).

25 [0223] Step 7: HMNR (CD₃OD) δ 1.92-1.96 (m, 1H), 2.54-2.60 (m, 1H), 3.22 (d, J = 11.51 Hz, 1H), 3.41-3.49 (m, 1H), 3.56 (dd, J = 4.35 Hz and 12.75 Hz, 1H), 3.86 (d, J = 11.50 Hz, 1H), 4.10 (dd, J = 4.98 Hz and 11.20 Hz, 1H), 5.31 (s, 2H), 7.23 (d, J = 8.71 Hz, 2H), 7.36-7.39 (m, 2H), 7.47-7.48 (m, 1H), 7.58-7.6 (m, 1H), 7.90 (d, J = 8.71, 2H).

30 [0224] The compounds of Table 1 were prepared by the method of Example 1 substituting the appropriate benzyl halide in step 6.

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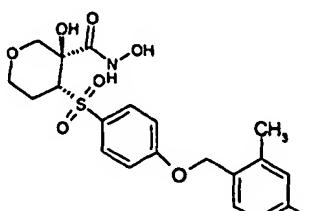
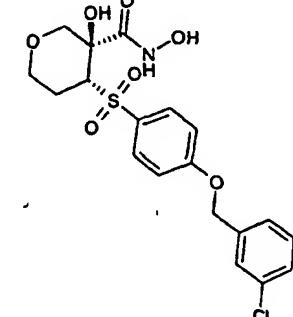
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TABLE 1

| Example | Structure | Name | Yield (%) | Mass Spec ($[M+H]^+$) |
|---------|---|---|-----------|-------------------------|
| 2 |  | 4-[4-(4-Fluoro-2-methyl-benzyloxy)-benzenesulfonyl]-3-hydroxy-tetrahydro-pyran-3-carboxylic acid hydroxyamide | 25 | 440 |
| 3 |  | 4-[4-(3-Chloro-benzyloxy)-benzenesulfonyl]-3-hydroxy-tetrahydro-pyran-3-carboxylic acid hydroxyamide | 13 | 442 |

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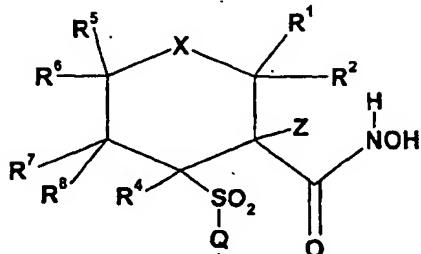
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| Example | Structure | Name | Yield (%) | Mass Spec ([M+H] ⁺) |
|---------|-----------|--|-----------|---------------------------------|
| 4 | | 4-[4-(4-Chloro-benzyloxy)-benzenesulfonyl]-3-hydroxy-tetrahydro-pyran-3-carboxylic acid hydroxyamide | 14 | 442 |
| 5 | | 4-[4-(2-Chloro-benzyloxy)-benzenesulfonyl]-3-hydroxy-tetrahydro-pyran-3-carboxylic acid hydroxyamide | 17 | 442 |
| 6 | | 4-[4-(3-Fluoro-benzyloxy)-benzenesulfonyl]-3-hydroxy-tetrahydro-pyran-3-carboxylic acid hydroxyamide | 18 | 426 |
| 7 | | 3-Hydroxy-4-[4-(2-methyl-benzyloxy)-benzenesulfonyl]-tetrahydro-pyran-3-carboxylic acid hydroxyamide | 34 | 422 |

| Example | Structure | Name | Yield (%) | Mass Spec ([M+H] ⁺) |
|---------|-----------|--|-----------|---------------------------------|
| 8 | | 4-[4-(4-Fluoro-2-methylbenzyl)oxy]-3-hydroxy-tetrahydro-pyran-3-carboxylic acid hydroxyamide | 46 | 440 |

Claims

20 1. A compound of the formula



35 or a pharmaceutically acceptable salt thereof, wherein

X is oxygen, sulfur, >SO, >SO₂ or >NR³;

40 Z is -OR¹¹, -NR¹²R¹³ or (C₁-C₆)alkyl optionally substituted with one to three substituents independently selected from the group consisting of halo, hydroxy, -CN, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₆-C₁₀)aryl(C₂-C₆)alkenyl, (C₁-C₉)heteroaryl(C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₆-C₁₀)aryl(C₂-C₆)alkynyl, (C₁-C₉)heteroaryl(C₂-C₆)alkynyl, amino, (C₁-C₆)alkylamino, [(C₁-C₆)alkyl]₂amino, mercapto, (C₁-C₆)alkylthio, (C₁-C₆)alkoxy, perfluoro (C₁-C₆)alkyl, perfluoro(C₁-C₆)alkoxy, (C₆-C₁₀)aryl, (C₁-C₉)heteroaryl, (C₃-C₉)heterocyclic, (C₃-C₉)cycloalkyl, (C₆-C₁₀)arylamino, (C₆-C₁₀)arylthio, (C₆-C₁₀)aryloxy, (C₁-C₉)heteroarylthio, (C₁-C₉)heteroaryloxy, (C₃-C₉)heterocyclic-amino, (C₃-C₉)heterocyclic-S-, (C₃-C₉)heterocyclic-O-, (C₃-C₉)cycloalkylamino, (C₃-C₉)cycloalkyl-S-, (C₃-C₉)cycloalkyl-O-, (C₁-C₆)alkyl-(C=O)-, (C₁-C₆)alkyl-(C=O)-NH-, (C₁-C₆)alkyl-(C=O)-S-, (C₁-C₆)alkyl-(C=O)-O-, (C₁-C₆)alkoxy-(C=O)-, -CO₂H, H₂N-(C=O)-, (C₁-C₆)alkyl-NH-(C=O)- and [(C₁-C₆)alkyl]₂-N-(C=O)-;

50 R¹, R², R⁵ and R⁶ are each independently selected from the group consisting of hydrogen, -CN, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₆-C₁₀)aryl(C₂-C₆)alkenyl, (C₁-C₉)heteroaryl(C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₆-C₁₀)aryl(C₂-C₆)alkynyl, (C₁-C₉)heteroaryl(C₂-C₆)alkynyl, perfluoro(C₁-C₆)alkyl, (C₆-C₁₀)aryl, (C₁-C₉)heteroaryl, (C₃-C₆)cycloalkyl, (C₃-C₉)heterocyclic, (C₁-C₆)alkyl-(C=O)-, (C₁-C₆)alkoxy-(C=O)-, -CO₂H, H₂N-(C=O)-, (C₁-C₆)alkyl-NH-(C=O)- and [(C₁-C₆)alkyl]₂-N-(C=O)-;

55 wherein said R¹, R², R⁵ and R⁶ (C₁-C₆)alkyl groups are each independently optionally substituted by one to three groups selected from halo, trifluoromethyl, hydroxy, amino, -CN, (C₁-C₆)alkylthio, (C₁-C₆)alkoxy, (C₆-C₁₀)aryl, (C₁-C₉)heteroaryl, (C₃-C₆)cycloalkyl, (C₃-C₉)heterocyclic, (C₆-C₁₀)arylamino, (C₆-C₁₀)arylthio, (C₆-C₁₀)aryloxy, (C₁-C₉)heteroarylthio, (C₁-C₉)heteroaryloxy, (C₃-C₉)heterocyclic-amino, (C₃-C₉)heterocyclic-S-, (C₃-C₉)heterocyclic-O-, (C₃-C₉)cycloalkylamino, (C₃-C₉)cycloalkyl-S-, (C₃-C₉)cycloalkyl-O-, (C₆-C₁₀)aryl(C₁-C₂)alkoxy, (C₁-C₉)heteroaryl(C₁-C₂)alkoxy, (C₁-C₆)alkyl-(C=O)-NH-, (C₁-C₆)

alkyl-(C=O)-S-, (C₁-C₆)alkyl-(C=O)-O-, (C₁-C₆)alkylsulfinyl, (C₆-C₁₀)arylsulfinyl, (C₁-C₆)alkylsulfonyl, (C₆-C₁₀)arylsulfonyl, (C₁-C₆)alkylamino, or ((C₁-C₆)alkyl)₂amino;

R³ is hydrogen; (C₁-C₆)alkyl optionally substituted by one or more of -CN, perfluoro(C₁-C₆)alkyl, (C₆-C₁₀)aryl, (C₃-C₆)cycloalkyl, (C₁-C₆)alkyl(C=O)-, (C₁-C₆)alkoxy-(C=O)-, -CO₂H, (C₁-C₆)alkyl-NH-(C=O)-, and [(C₁-C₆)alkyl]₂-N-(C=O)-; (C₆-C₁₀)arylsulfonyl; (C₁-C₆)alkylsulfonyl; (C₁-C₆)alkyl-NH-(C=O)-; [(C₁-C₆)alkyl]₂-N-(C=O)-; or (R¹⁰R⁹N)-(C=O)-; wherein R⁹ and R¹⁰ are taken together with the nitrogen to which they are attached to form a ring selected from azetidinyl, pyrrolidinyl, piperidinyl, morpholinyl and thiomorphonyl;

R⁴ is hydrogen or (C₁-C₄)alkyl;

R^7 and R^8 are each independently selected from the group consisting of hydrogen, hydroxy, halo, -CN, (C_1 - C_6)alkyl, (C_2 - C_6)alkenyl, (C_2 - C_6)alkynyl, amino, (C_1 - C_6)alkylamino, $[(C_1$ - C_6)alkyl] $_2$ amino, (C_1 - C_6)alkylthio, (C_1 - C_6)alkoxy, perfluoro(C_1 - C_6)alkyl, perfluoro(C_1 - C_6)alkoxy, (C_3 - C_8)cycloalkyl, (C_6 - C_{10})aryl, (C_3 - C_9)heterocyclic, (C_1 - C_9)heteroaryl, (C_6 - C_{10})aryl amino, (C_6 - C_{10})arylthio, (C_6 - C_{10})aryloxy, (C_1 - C_9)heteroaryl amino, (C_1 - C_9)heteroarylthio, (C_1 - C_9)heteroaryl oxy, (C_3 - C_9)heterocyclic-amino, (C_3 - C_9)heterocyclic-S-, (C_3 - C_9)heterocyclic-O-, (C_3 - C_9)cycloalkylamino, (C_3 - C_9)cycloalkyl-S-, (C_3 - C_9)cycloalkyl-O-, (C_6 - C_{10})aryl(C_2 - C_6)alkenyl, (C_1 - C_9)heteroaryl(C_2 - C_6)alkenyl, (C_6 - C_{10})aryl(C_2 - C_6)alkynyl, (C_1 - C_9)heteroaryl(C_2 - C_6)alkynyl, (C_1 - C_6)alkyl(C=O)-, (C_1 - C_6)alkyl(C=O)-NH-, (C_1 - C_6)alkyl(C=O)-S-, (C_1 - C_6)alkyl(C=O)-O-, (C_1 - C_6)alkoxy(C=O)-, -CO₂H, H₂N-(C=O)-, (C_1 - C_6)alkyl-NH-(C=O)- and $[(C_1$ - C_6)alkyl] $_2$ -N-(C=O)-;

wherein each of said R⁷ and R⁸ (C₁-C₆)alkyl group are independently optionally substituted by one to three substituents independently selected from halo, hydroxy, -CN, (C₁-C₆)alkoxy, (C₁-C₆)alkylthio, trifluoromethyl, (C₃-C₆)cycloalkyl, (C₆-C₁₀)aryl, (C₃-C₉)heterocyclic, (C₁-C₉)heteroaryl, (C₆-C₁₀)arylamino, (C₆-C₁₀)arylthio, (C₆-C₁₀)aryloxy, (C₁-C₉)heteroaryl amino, (C₁-C₉)heteroarylthio, (C₁-C₉)heteroaryloxy, (C₃-C₉)heterocyclic-amino, (C₃-C₉)heterocyclic-S-, (C₃-C₉)heterocyclic-O-, (C₃-C₉)cycloalkylamino, (C₃-C₉)cycloalkyl-S-, (C₃-C₉)cycloalkyl-O-, (C₆-C₁₀)aryl(C₁-C₂)alkoxy, (C₁-C₉)heteroaryl(C₁-C₂)alkoxy, (C₁-C₆)alkyl(C=O)-NH-, (C₁-C₆)alkyl(C=O)-S-, (C₁-C₆)alkyl(C=O)-O-, (C₁-C₆)alkylsulfinyl, (C₆-C₁₀)arylsulfinyl, (C₁-C₆)alkylsulfonyl, (C₆-C₁₀)arylsulfonyl, amino, (C₁-C₆)alkylamino and ((C₁-C₆)alkyl)₂amino;

or R¹ and R², R⁵ and R⁶ or R⁷ and R⁸ may be taken together to form a carbonyl group or an optionally substituted (C₃-C₆)cycloalkyl ring optionally containing 1 or 2 heteroatoms; wherein said heteroatoms may be selected from the group consisting of -S-, -O- or >NH or >N(C₁-C₆)alkyl; and said optional substituents (i.e. 1-3 substituents per ring) may be selected from (C₁-C₄)alkyl, fluoro, chloro, hydroxy, (C₁-C₄)alkoxy and -NR14R15.

or R⁵ and R⁷, R⁵ and R⁸, R⁶ and R⁷ or R⁶ and R⁸ may be taken together to form an optionally substituted (C₄-C₆)cycloalkyl ring optionally containing 1 or 2 heteroatoms; wherein said heteroatoms may be selected from the group consisting of -S-, -O- or >NH or >N(C₁-C₆)alkyl; and said optional substituents (i.e. 1-3 substituents) may be selected from (C₁-C₄)alkyl, fluoro, chloro, hydroxy, (C₁-C₄)alkoxy and -NR¹⁴R¹⁵;

R¹¹ is hydrogen, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₆-C₁₀)aryl(C₂-C₆)alkenyl, (C₂-C₉)heteroaryl(C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₆-C₁₀)aryl(C₂-C₆)alkynyl, (C₁-C₉)heteroaryl(C₂-C₆)alkynyl, perfluoro(C₁-C₆)alkyl, (C₆-C₁₀)aryl, (C₁-C₉)heteroaryl, (C₃-C₆)cycloalkyl, (C₃-C₉)heterocyclic, (C₁-C₆)alkyl-(C=O)-, (C₁-C₆)alkoxy-(C=O)-, (C₁-C₆)alkyl-NH-(C=O)- or [(C₁-C₆)alkyl]2-N-(C=O)-;

R¹² is hydrogen, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₆-C₁₀)aryl(C₂-C₆)alkenyl, (C₁-C₉)heteroaryl(C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₆-C₁₀)aryl(C₂-C₆)alkynyl, (C₁-C₉)heteroaryl(C₂-C₆)alkynyl, perfluoro(C₁-C₆)alkyl, (C₆-C₁₀)aryl, (C₁-C₉)heteroaryl, (C₃-C₆)cycloalkyl, (C₃-C₉)heterocyclic, (C₁-C₆)alkyl-(C=O)-, (C₁-C₆)alkoxy-(C=O)-, H₂N-(C=O)-, (C₁-C₆)alkyl-NH-(C=O)- or [(C₁-C₆)alkyl]₂-N-(C=O)-;

R^{13} is hydrogen, (C_1-C_6) alkyl, (C_2-C_6) alkenyl, (C_6-C_{10}) aryl (C_2-C_6) alkenyl, (C_1-C_9) heteroaryl (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, (C_6-C_{10}) aryl (C_2-C_6) alkynyl, (C_1-C_9) heteroaryl (C_2-C_6) alkynyl, perfluoro (C_1-C_6) alkyl, (C_6-C_{10}) aryl, (C_1-C_9) heteroaryl, (C_6-C_9) cycloalkyl or (C_6-C_9) heterocyclic;

R^{14} is hydrogen, (C_1-C_6) alkyl, (C_2-C_6) alkenyl, (C_6-C_{10}) aryl (C_2-C_6) alkenyl, (C_1-C_9) heteroaryl (C_2-C_6) alkenyl,

(C₂-C₆)alkynyl, (C₆-C₁₀)aryl(C₂-C₆)alkynyl, (C₁-C₉)heteroaryl(C₂-C₆)alkynyl, perfluoro(C₁-C₆)alkyl, (C₆-C₁₀)aryl, (C₁-C₉)heteroaryl, (C₃-C₆)cycloalkyl, (C₃-C₉)heterocyclic, (C₁-C₆)alkyl-(C=O)-, (C₁-C₆)alkoxy-(C=O)-, H₂N-(C=O)-, (C₁-C₆)alkyl-NH-(C=O)- or [(C₁-C₆)alkyl]₂-N-(C=O)-;

R^{15} is hydrogen, (C_1-C_6) alkyl, (C_2-C_6) alkenyl, (C_6-C_{10}) aryl (C_2-C_6) alkenyl, (C_1-C_9) heteroaryl (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, (C_6-C_{10}) aryl (C_2-C_6) alkynyl, (C_1-C_9) heteroaryl (C_2-C_6) alkynyl, perfluoro (C_1-C_6) alkyl, (C_6-C_{10}) aryl, (C_1-C_9) heteroaryl, (C_3-C_6) cycloalkyl or (C_3-C_9) heterocyclic;

Q is (C₁-C₆)alkyl, (C₆-C₁₀)aryl, (C₁-C₉)heteroaryl, (C₃-C₉)heterocyclic, (C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₁-C₉)heteroaryl(C₁-C₆)alkyl, (C₃-C₉)heterocyclic(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₆-C₁₀)aryl, (C₆-C₁₀)aryl(C₁-C₉)heteroaryl, (C₆-C₁₀)aryl(C₃-C₉)heterocyclic, (C₁-C₉)heteroaryl(C₆-C₁₀)aryl, (C₁-C₉)heteroaryl(C₁-C₉)heteroaryl, (C₁-C₉)heteroaryl(C₃-C₉)heterocyclic, (C₃-C₉)heterocyclic(C₆-C₁₀)aryl, (C₃-C₉)heterocyclic(C₁-C₉)heteroaryl, (C₃-C₉)heterocyclic(C₃-C₉)heterocyclic, (C₆-C₁₀)aryloxy(C₁-C₆)alkyl, (C₆-C₁₀)aryloxy(C₆-C₁₀)aryl, (C₆-C₁₀)aryloxy(C₁-C₆)heteroaryl, (C₆-C₁₀)aryloxy(C₂-C₆)heterocyclic, (C₁-C₉)heteroaryloxy(C₁-C₆)alkyl, (C₁-C₉)het-

2. A compound according to claim 1, wherein X is -O-.
3. A compound according to claim 1, wherein Z is -OR¹¹.
4. A compound according to claim 1, wherein Q is 4-((C₆-C₁₀)aryl(C₁-C₆)alkoxy)-(C₆-C₁₀)aryl, 4-((C₆-C₁₀)aryl(C₁-C₆)alkoxy)-(C₂-C₉)heteroaryl, 4-((C₂-C₉)heteroaryl(C₁-C₆)alkoxy)-(C₆-C₁₀)aryl, 4-((C₂-C₉)heteroaryl(C₁-C₆)alkoxy)-(C₂-C₉)heteroaryl; wherein each of said Q aryl or heteroaryl moieties may optionally be substituted by one or more substituents independently selected from halo, (C₁-C₆)alkyl, (C₁-C₆)alkoxy or perfluoro(C₁-C₃)alkyl.
5. A compound according to claim 1, wherein R¹, R², R⁵ and R⁶ are each independently selected from the group consisting of hydrogen, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, perfluoro(C₁-C₆)alkyl, (C₁-C₆)alkyl(C=O)-, (C₁-C₆)alkoxy-(C=O)-, (C₁-C₆)alkyl-NH-(C=O)-, and [(C₁-C₆)alkyl]₂N-(C=O)-; wherein each of said (C₁-C₆)alkyl groups are each independently optionally substituted by one to two groups selected from halo, trifluoromethyl, hydroxy, amino, (C₁-C₆)alkoxy, (C₆-C₁₀)aryl, (C₁-C₉)heteroaryl, (C₃-C₆)cycloalkyl, (C₃-C₉)heterocyclic, (C₁-C₆)alkyl-(C=O)-NH-, (C₁-C₆)alkyl-(C=O)-O-, (C₁-C₆)alkylamino or ((C₁-C₆)alkyl)₂amino.

6. A compound according to claim 1, wherein R⁷ and R⁸ are each independently selected from the group consisting of hydrogen, hydroxy, halo, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, amino, (C₁-C₆)alkylamino, [(C₁-C₆)alkyl]₂amino, (C₁-C₆)alkoxy, perfluoro(C₁-C₆)alkyl and perfluoro(C₁-C₆)alkoxy.

5 7. A compound according to claim 1, wherein R¹-R⁸ are all each hydrogen.

8. A compound according to claim 1, wherein said compound is selected from the group consisting of:

10 4-[4-(4-Fluoro-2-methyl-benzyl)oxy]-benzenesulfonyl]-3-hydroxy-tetrahydro-pyran-3-carboxylic acid hydroxyamide;

4-[4-(3-Chloro-benzyl)oxy]-benzenesulfonyl]-3-hydroxy-tetrahydro-pyran-3-carboxylic acid hydroxyamide;

4-[4-(4-Chloro-benzyl)oxy]-benzenesulfonyl]-3-hydroxy-tetrahydro-pyran-3-carboxylic acid hydroxyamide;

4-[4-(2-Chloro-benzyl)oxy]-benzenesulfonyl]-3-hydroxy-tetrahydro-pyran-3-carboxylic acid hydroxyamide;

15 4-[4-(3-Fluoro-benzyl)oxy]-benzenesulfonyl]-3-hydroxy-tetrahydro-pyran-3-carboxylic acid hydroxyamide;

3-Hydroxy-4-[4-(2-methyl-benzyl)oxy]-benzenesulfonyl]-tetrahydro-pyran-3-carboxylic acid hydroxyamide;

and

4-[4-(4-Fluoro-2-methyl-benzyl)oxy]-benzenesulfonyl]-3-hydroxy-tetrahydro-pyran-3-carboxylic acid hydroxyamide.

20 9. A compound of formula I, as defined in claim 1, or a pharmaceutically acceptable salt thereof, for use as a pharmaceutical.

10. A pharmaceutical composition comprising a compound of formula I, as defined in claim 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

25 11. A pharmaceutical composition for the treatment of a condition selected from arthritis, inflammatory bowel disease, Crohn's disease, emphysema, acute respiratory distress syndrome, asthma, chronic obstructive pulmonary disease, Alzheimer's disease, organ transplant toxicity, cachexia, allergic reactions, allergic contact hypersensitivity, cancer, tissue ulceration, restenosis, periodontal disease, epidermolysis bullosa, osteoporosis, loosening of artificial joint implants, atherosclerosis, aortic aneurysm, congestive heart failure, myocardial infarction, stroke, cerebral ischemia, head trauma, spinal cord injury, neuro-degenerative disorders, autoimmune disorders, Huntington's disease, Parkinson's disease, migraine, depression, peripheral neuropathy, pain, cerebral amyloid angiopathy, nootropic or cognition enhancement, amyotrophic lateral sclerosis, multiple sclerosis, ocular angiogenesis, corneal injury, macular degeneration, abnormal wound healing, burns, diabetes, tumor invasion, tumor growth, tumor metastasis, corneal scarring, scleritis, AIDS, sepsis and septic shock in a mammal, comprising an amount of a compound of formula I, as defined in claim 1, or a pharmaceutically acceptable salt thereof, effective in such treatments or inhibition and a pharmaceutically acceptable carrier.

30 12. Use of a compound of formula I, as defined in claim 1, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a condition selected from the group consisting of arthritis, inflammatory bowel disease, Crohn's disease, emphysema, acute respiratory distress syndrome, asthma, chronic obstructive pulmonary disease, Alzheimer's disease, organ transplant toxicity, cachexia, allergic reactions, allergic contact hypersensitivity, cancer, tissue ulceration, restenosis, periodontal disease, epidermolysis bullosa, osteoporosis, loosening of artificial joint implants, atherosclerosis, aortic aneurysm, congestive heart failure, myocardial infarction, stroke, cerebral ischemia, head trauma, spinal cord injury, neuro-degenerative disorders, autoimmune disorders, Huntington's disease, Parkinson's disease, migraine, depression, peripheral neuropathy, pain, cerebral amyloid angiopathy, nootropic or cognition enhancement, amyotrophic lateral sclerosis, multiple sclerosis, ocular angiogenesis, corneal injury, macular degeneration, abnormal wound healing, burns, diabetes, tumor invasion, tumor growth, tumor metastasis, corneal scarring, scleritis, AIDS, sepsis and septic shock.

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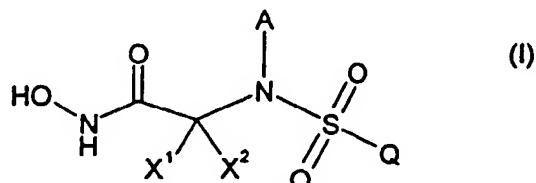
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(54) alpha-sulfonylamino hydroxamic acid inhibitors of matrix metallo-proteinases for the treatment of peripheral or central nervous system disorders

(57) The present invention relates to a method of using a compound of the formula (I):



wherein A, X¹, X², and Q are as defined herein, a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof, in the treatment of a disease, condition or disorder of the peripheral or central nervous system, including but not limited to Alzheimer's disease, stroke/cerebral ischemia, head trauma, spinal cord injury, multiple sclerosis, amyotrophic lateral sclerosis, Huntington's disease, Parkinson's disease, migraine, cerebral amyloid angiopathy, AIDS, age-related cognitive decline, mild cognitive impairment and prion diseases.

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DescriptionBackground of the Invention

5 [0001] The present invention relates to new methods of using certain α -sulfonylamino hydroxamic acid inhibitors of matrix metalloproteinases in the treatment of diseases, conditions and disorders of the peripheral or central nervous system, including but not limited to Alzheimer's disease, stroke/cerebral ischemia, head trauma, spinal cord injury, multiple sclerosis, amyotrophic lateral sclerosis, Huntington's disease, Parkinson's disease, migraine, cerebral amyloid angiopathy, AIDS, age-related cognitive decline; mild cognitive impairment and prion diseases, and pharmaceutical compositions useful therefor.

10 [0002] The compounds of the present invention are inhibitors of zinc metalloendopeptidases, especially those belonging to the matrix metalloproteinase (also called MMP or matrixin) and repprolysin (also known as adamylsin) sub-families of the metzincins (Rawlings, *et al.*, Methods in Enzymology, 248, 183-228 (1995) and Stocker, *et al.*, Protein Science, 4, 823-840 (1995)).

15 [0003] The MMP subfamily of enzymes, currently contains seventeen members (MMP-1, MMP-2, MMP-3, MMP-7, MMP-8, MMP-9, MMP-10, MMP-11, MMP-12, MMP-13, MMP-14, MMP-15, MMP-16, MMP-17, MMP-18, MMP-19, MMP-20). The MMP's are most well known for their role in regulating the turn-over of extracellular matrix (ECM) proteins and as such play important roles in normal physiological processes such as reproduction, development and differentiation.

20 [0004] In the central nervous system, the ECM not only serves structural and adhesive functions but also stimulates intracellular signaling pathways in response to association of the matrix with cell surface proteins. (Yong *et al.*, Trends in Neuroscience, 21, 75-80 (1998)) Excessive expression of MMP's is believed to contribute to the pathogenesis of tissue destructive diseases such as arthritis, multiple sclerosis (MS) and cancer, conditions where inflammation and invasive processes play important roles. In Alzheimer's Disease (AD) and age-matched control samples, the expression of MMP's, particularly MMP-9 and MMP-2, is increased. The link between MMP's, AD and the ECM is supported by *in vitro* and *in vivo* evidence. In clinical samples taken from stroke, MS, amyotrophic lateral sclerosis (ALS) patients, increased expression of MMP's has also been documented. In AD, astrocytes produce inflammatory mediators and ECM proteins which surround neuritic plaques.

25 [0005] Like other members of the matrix metalloproteinase family, MMP-2 (72kDa type IV collagenase or Gelatinase A) and MMP-9 (92kDa type IV collagenase or Gelatinase B) are calcium-requiring, zinc containing endopeptidases which are secreted from cells in a latent pro-enzyme form (Yong *et al.*, *supra*). These MMP's attack type IV collagen, laminen and fibronectin, the major components of the ECM surrounding cerebral blood vessels. Because of the dire consequences of inappropriate or unbalanced activity, they are tightly regulated by three independent mechanisms: proenzyme activation, gene transcription and inhibition by their endogenous inhibitor TIMP-1 (Borden and Heller, Critical Reviews in Eukaryotic Gene Expression, 7, 159-178, (1997)). The expression of MMP-9 is induced by growth factors and inflammatory cytokines in an NF-KB and AP-1 dependent manner (Bond *et al.*, FEBS Letters, 435, 29-34, (1998)). MMP-2 is generally constitutively expressed; however, its mRNA can be modulated by some of the same factors which modulate MMP-9 expression (Gottschall and Deb, Neuroimmunomodulation, 3, 69-75, (1996)).

30 [0006] Additionally, in AD hippocampus, MMP-9 protein is increased as much as fourfold (Backstrom *et al.*, J. Neurochemistry, 58, 983-92 (1992)). The enzyme is predominantly found in its latent or proenzyme form in close proximity to extracellular amyloid plaques (Backstrom *et al.*, J. Neuroscience, 16, 7910-19 (1996)). Similar observations were made in aged beagles. In amyloid-positive samples, statistically significant increases in latent MMP-9 were seen as compared with amyloid-negative samples (Lim *et al.*, J. Neurochemistry, 68, 1606-11 (1997)).

35 [0007] The link between MMPs, AD and the ECM is supported by additional evidence (Perlmuter *et al.*, J. Neuroscience Res., 30, 673-81 (1991); Brandan and Inestrosa, Gen. Pharmacology, 24, 1063-8 (1993); Eikelenboom *et al.*, Virchows Archiv, 424, 421-7 (1994); Luckenbill-Edds, Brain Res. Revs., 23, 1-27 (1997)). Laminin is induced by brain injury and co-localizes with amyloid deposits in AD. In AD tissue, native human laminin was localized in large punctate, extracellular deposits which co-localize with plaques. Antibodies to the neurite-outgrowth promoting domains of laminin B2 or A chains localize to glia or capillary basement membranes, respectively. In control brains, laminin immunoreactivity is only found in capillaries (Murtomaki *et al.*, J. Neuroscience Res., 32, 261-73 (1993)). In a murine model of neurodegeneration (Chen and Strickland, Cell, 91, 917-25 (1997)), kainic acid challenged neurons secrete tPA. This initiates a cascade of proteolytic events beginning with conversion of plasminogen to plasmin and ending with degradation of laminin and subsequent death of neurons. Plasmin is a known activator of MMP-9 which could be part of this proteolytic cascade resulting in the eventual destruction of neurons.

40 [0008] In PC12 cells, laminin or specific laminin peptides are capable to stimulating MMP secretion and this mechanism is linked to laminin-mediated neurite outgrowth (Weeks *et al.*, Exp. Cell Res., 243, 375-82 (1998)). There has been a suggestion that these specific laminin sites may only be exposed in the basement membrane as observed in AD (Kibby *et al.*, Proc. Nat. Acad. Sci., 90, 10150-3 (1993)). Further deposition of A β could be nucleated by these

laminin fragments which are found in neuritic plaques. Therefore, interfering with degradation of laminin could have the outcome of preserving the ECM, enhancing neuronal survival, and eliminating at least one protein which may act as a seed for nucleation of A β .

[0009] Elevated expression of MMP-9 and MMP-2 has also been documented in stroke, MS and ALS. After focal ischemia in humans, MMP-9 is markedly elevated in the infarcted tissue at two days post-infarction and remained elevated for months. Increases in MMP-2 were subtle at 2-5 days and like MMP-9, remained marked and significant for months (Clark *et al.*, *Neuroscience Letters*, 238, 53-6 (1997)). Analysis of brain and spinal cord samples from ALS patients identified major bands of enzyme activity as MMP-2 and MMP-9; MMP-2 in astrocytes and MMP-9 in pyramidal neurons of the motor cortex and motor neurons of the spinal cord. Increases in MMP-9 were observed in ALS frontal and occipital cortices and spinal cord versus control samples. The high level of MMP-9 and its possible release at the synapse may destroy the structural integrity of the surrounding matrix thereby contributing to the pathogenesis of ALS. (Lim *et al.*, *J. Neurochemistry*, 67, 251-9 (1996)). MMP-9 is elevated in CSF of MS patients and is detected by immunohistochemistry in active and chronic lesions. In autopsied samples from normal brain, MMP-like immunoreactivity (MMP-1, -2, -3 and -9) is localized to microglia and astrocytes. In MS patient samples, MMP expression is up-regulated in these glial cells and also in perivascular macrophages that are present in active brain lesion. (Chandler *et al.*, *J. Neuroimmunology*, 72, 155-61 (1997); Liedtke *et al.*, *Annals of Neurology*, 44, 35-46 (1998).)

[0010] In addition to the foregoing, MMP's have been associated with neuronal degeneration in a number of animal models. These models can be used in an MMP inhibitor program to track inhibitor activity and predict pre-clinical efficacy. After focal ischemia in rats, MMP-9 was shown to increase in the infarcted area during the first day (Rosenberg *et al.*, *J. Cerebral Blood Flow & Metabolism*, 16, 360-6, (1996)). MMP-2 remained the same until 5 days after injury when it increased significantly. This time course of induction is very similar to that seen by Clark *et al*, *supra*, in human clinical stroke samples. (Rosenberg and Navratil, *Neurology*, 48, 921-6 (1997)) have also shown that metalloproteinase inhibition blocks edema in intracerebral hemorrhage in the rat. A model of direct injection of MMP's into the rat brain also demonstrated neuronal loss after MMP-9 or -2, but not MMP-8, injection as well as the loss of GFAP and myelin immunoreactivity (Anthony *et al.*, *J. Neuroimmunology*, 87, 62-72 (1998)).

[0011] MMP-9 was detected in the CSF of mice with Experimental Autoimmune Encephalomyelitis (EAE), an animal model for MS. A hydroxamate inhibitor of MMP, GM6001, was found to suppress the development of, or reverse established, EAE (Gijbels, *J. Clinical Invest.*, 94, 2177-82 (1994)). Based on this model, MMP inhibitors might act by preventing the influx of inflammatory cells across the basement membrane or ECM barrier that surrounds cerebral endothelium. Another hydroxamic acid-based compound which is a combined inhibitor of MMP and TNF- α processing/release, BB-1101 (Redford *et al.*, *Brain*, 120, 1895-905 (1997)), attenuates Experimental Autoimmune Neuritis (EAN), a model of Guillain-Barre syndrome.

[0012] Lastly, *in vitro* experiments suggest a role for MMP's in the development or progression of neuritic plaques. Deb and Gottschall, *J. Neurochemistry*, 66, 1641-7 (1996)), demonstrated that A β induces MMP-9 and -2 expression in astrocyte and mixed hippocampal cultures. Further, MMP-9 induction by A β in rat microglia can be inhibited by the anti-inflammatory agents dexamethasone and indomethacin (Gottschall, *Neuroreport*, 7, 3077-80 (1996)). This is of particular importance when considered in conjunction with clinical data which suggests that administration of anti-inflammatory drugs may slow the progression of AD (Rogers *et al.*, *Arzneimittelforschung*, 45, 439-42 (1995)).

[0013] Applicants now disclose a method of treatment of diseases, conditions or disorders of the peripheral and central nervous system, including but not limited to Alzheimer's disease, stroke/cerebral ischemia, head trauma, spinal cord injury, multiple sclerosis, amyotrophic lateral sclerosis, Huntington's disease, Parkinson's disease, migraine, cerebral amyloid angiopathy, AIDS, age-related cognitive decline; mild cognitive impairment and prion diseases, comprising the administration of small molecule inhibitors of MMP-9, MMP-2 or mixed MMP inhibitors which may reduce neuronal damage and limit neuroinflammation.

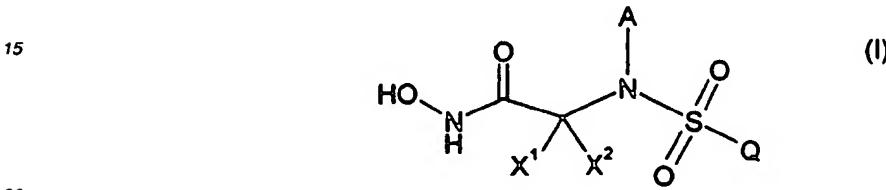
[0014] However, the diseases in which inhibition of MMP's will provide therapeutic benefit include but are not limited to: arthritis (including osteoarthritis and rheumatoid arthritis), inflammatory bowel disease, Crohn's disease, emphysema, acute respiratory distress syndrome, asthma chronic obstructive pulmonary disease, Alzheimer's disease, organ transplant toxicity, cachexia, allergic reactions, allergic contact hypersensitivity, cancer, tissue ulceration, restenosis, periodontal disease, epidermolysis bullosa, osteoporosis, loosening of artificial joint implants, atherosclerosis (including atherosclerotic plaque rupture), aortic aneurysm (including abdominal aortic aneurysm and brain aortic aneurysm), congestive heart failure, myocardial infarction, stroke, cerebral ischemia, head trauma, spinal cord injury, neurodegenerative disorders (acute and chronic), inflammatory and autoimmune disorders, Huntington's disease, Parkinson's disease, migraine, depression, peripheral neuropathy, pain, cerebral amyloid angiopathy, nootropic or cognition enhancement, amyotrophic lateral sclerosis, multiple sclerosis, ocular angiogenesis, corneal injury, macular degeneration, abnormal wound healing, burns, diabetes, tumor invasion, tumor growth, tumor metastasis, corneal scarring, scleritis, AIDS, sepsis, septic shock and other diseases characterized by metalloproteinase or ADAM expression. This invention also relates to methods of using the hydroxamic acid compounds described herein in the treatment of the above-identified diseases, conditions and disorders in mammals, especially humans, and to the pharmaceutical compositions

containing these compounds useful in such methods.

[0015] It is recognized that different combinations of MMP's are expressed in different pathological situations. As such inhibitors with specific selectivities for individual MMP's may be preferred for individual diseases.

5 Summary of the Invention

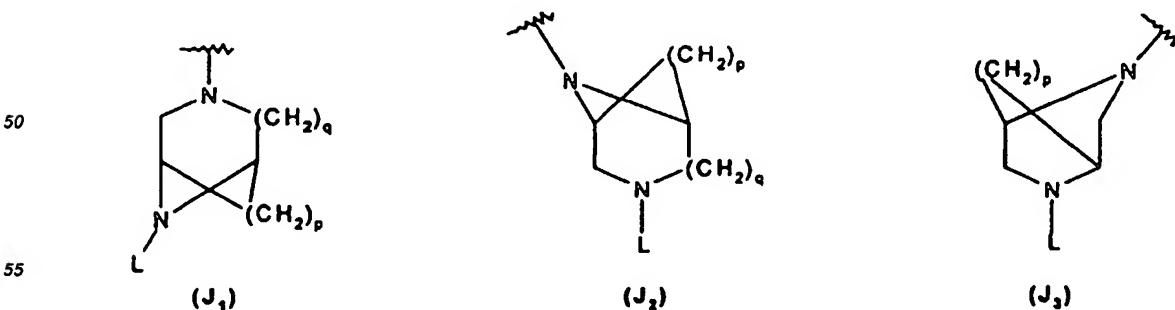
[0016] The present invention relates to a method of treating a disease or disorder of the peripheral or central nervous system, including but not limited to Alzheimer's disease, stroke/cerebral ischemia, head trauma, spinal cord injury, multiple sclerosis, amyotrophic lateral sclerosis, Huntington's disease, Parkinson's disease, migraine, cerebral amyloid 10 angiopathy, AIDS, age-related cognitive decline; mild cognitive impairment and prion diseases in a mammal, which comprises administering to said mammal a therapeutically effective amount of a compound of formula (I):

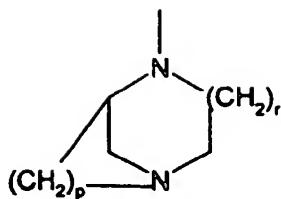


or the pharmaceutically acceptable salts thereof, wherein

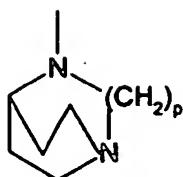
A is H or $-(CH_2)_n-(C=O)-Z$; where n is 0 to 6; and Z is hydroxy, (C_1-C_6) alkoxy or NR^1R^2 wherein R^1 and R^2 are each independently selected from the group consisting of hydrogen, (C_1-C_6) alkyl, piperidyl, (C_1-C_6) alkylpiperidyl, (C_6-C_{10}) arylpiperidyl, (C_2-C_9) heteroarylpiperidyl, (C_6-C_{10}) aryl(C_1-C_6)alkylpiperidyl, (C_1-C_6) acylpipeddyl, (C_6-C_{10}) aryl, (C_2-C_9) heteroaryl, (C_6-C_{10}) aryl(C_1-C_6)alkyl, (C_2-C_9) heteroaryl(C_1-C_6)alkyl, (C_6-C_{10}) aryl(C_6-C_{10})aryl, (C_6-C_{10}) aryl(C_6-C_{10})aryl(C_1-C_6)alkyl, (C_3-C_6) cycloalkyl, (C_3-C_6) cycloalkyl(C_1-C_6)alkyl, R^5 (C_2-C_6)alkyl, (C_1-C_5) alkyl(CHR^3)(C_1-C_6)alkyl wherein R^3 is hydroxy, (C_1-C_6) acyloxy, (C_1-C_6) alkoxy, piperazino, (C_1-C_6) acylamino, (C_1-C_6) alkylthio, (C_6-C_{10}) arylthio, (C_1-C_6) alkylsulfinyl, (C_6-C_{10}) arylsulfinyl, (C_1-C_6) alkylsulfoxyl, (C_6-C_{10}) arylsulfoxyl, amino, (C_1-C_6) acylamino, $((C_1-C_6)$ alkyl)₂ amino, (C_1-C_6) acylpiperazino, (C_1-C_6) alkylpiperazino, (C_6-C_{10}) aryl(C_1-C_6)alkylpiperazino, (C_2-C_9) heteroaryl(C_1-C_6)alkylpiperazino, morpholino, thiomorpholino, piperidino or pyrrolidino; R^4 (C_1-C_6)alkyl, (C_1-C_5) alkyl(CHR^4)(C_1-C_6)alkyl wherein R^4 is piperidyl, (C_1-C_6) alkylpiperidyl, (C_6-C_{10}) aryl(C_1-C_6)alkylpiperidyl, (C_2-C_9) heteroaryl(C_1-C_6)alkylpiperidyl or (C_2-C_9) heteroaryl(C_1-C_6)alkylpiperidyl; and $CH(R^5)COR^6$ wherein R^5 is hydrogen, (C_1-C_6) alkyl, (C_6-C_{10}) aryl(C_1-C_6)alkyl, (C_2-C_9) heteroaryl(C_1-C_6)alkyl, (C_1-C_6) alkylthio(C_1-C_6)alkyl, (C_6-C_{10}) arylthio(C_1-C_6)alkyl, (C_1-C_6) alkylsulfinyl(C_1-C_6)alkyl, (C_6-C_{10}) arylsulfinyl(C_1-C_6)alkyl, (C_1-C_6) alkylsulfonyl(C_1-C_6)alkyl, (C_6-C_{10}) arylsulfonyl(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, amino(C_1-C_6)alkyl, (C_1-C_6) acylamino(C_1-C_6)alkyl, $((C_1-C_6)$ acylamino)₂(C_1-C_6)alkyl, $R^7R^8NCO(C_1-C_6)$ alkyl or $R^7OCO(C_1-C_6)$ alkyl wherein R^7 and R^8 are each independently selected from the group consisting of hydrogen, (C_1-C_6) alkyl, (C_6-C_{10}) aryl(C_1-C_6)alkyl and (C_2-C_9) heteroaryl(C_1-C_6)alkyl; and R^6 is R^9O or $R^9R^{10}N$ wherein R^9 and R^{10} are each independently selected from the group consisting of hydrogen, (C_1-C_6) alkyl, (C_6-C_{10}) aryl(C_1-C_6)alkyl and (C_2-C_9) heteroaryl(C_1-C_6)alkyl; or R^1 and R^2 , or R^7 and R^8 , or R^9 and R^{10} may be taken together to form an azetidinyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, indolinyl, isoindolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, (C_1-C_6) acylpiperinyl, (C_1-C_6) alkylpiperazinyl, (C_6-C_{10}) aryl(piperazinyl, (C_2-C_9) heteroaryl(piperazinyl or a bridged diazabicycloalkyl ring selected from the group consisting of:

45





and



(J₄)

(J₅)

wherein p is 1, 2 or 3;

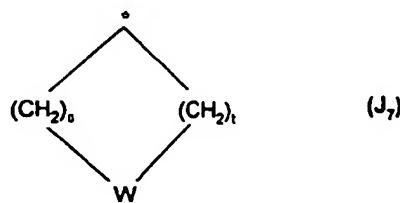
q is 1 or 2;

r is 0 or 1;

L is hydrogen, (C₁-C₃)alkyl or (C₁-C₆)acyl;

X^1 and X^2 are each independently selected from the group consisting of hydrogen, (C_1 - C_6)alkyl, trifluoromethyl, trifluoromethyl(C_1 - C_6)alkyl, (C_1 - C_6)alkyl (difluoromethylene), (C_1 - C_3)alkyl(difluoromethylene)(C_1 - C_3)alkyl, (C_6 - C_{10})aryl, (C_2 - C_9)heteroaryl, (C_6 - C_{10})aryl(C_1 - C_6)alkyl, (C_2 - C_9)heteroaryl(C_1 - C_6)alkyl, (C_6 - C_{10})aryl(C_6 - C_{10})aryl, (C_6 - C_{10})aryl(C_6 - C_{10})aryl(C_1 - C_6)alkyl, (C_3 - C_6)cycloalkyl, (C_3 - C_6)cycloalkyl(C_1 - C_6)alkyl, hydroxy(C_1 - C_6)alkyl, (C_1 - C_6)acyloxy(C_1 - C_6)alkyl, (C_1 - C_6)alkoxy(C_1 - C_6)alkyl, piperazinyl(C_1 - C_6)alkyl, (C_1 - C_6)acylamino(C_1 - C_6)alkyl, piperidyl, (C_1 - C_6)alkylpiperidyl, (C_6 - C_{10})aryl(C_1 - C_6)alkoxy(C_1 - C_6)alkyl, (C_2 - C_9)heteroaryl(C_1 - C_6)alkoxy(C_1 - C_6)alkyl, (C_1 - C_6)alkylthio(C_1 - C_6)alkyl, (C_6 - C_{10})arylthio(C_1 - C_6)alkyl, (C_1 - C_6)alkylsulfinyl(C_1 - C_6)alkyl, (C_6 - C_{10})aryl sulfinyl(C_1 - C_6)alkyl, (C_1 - C_6)alkylsulfonyl(C_1 - C_6)alkyl, (C_6 - C_{10})aryl sulfonyl(C_1 - C_6)alkyl, amino(C_1 - C_6)alkyl, (C_1 - C_6)alkylamino(C_1 - C_6)alkyl, ((C_1 - C_6)alkylamino)₂(C_1 - C_6)alkyl, $R^{11}CO(C_1-C_6)alkyl$ wherein R^{11} is $R^{12}O$ or $R^{12}R^{13}N$ wherein R^{12} and R^{13} are each independently selected from the group consisting of hydrogen, (C_1 - C_6)alkyl, (C_6 - C_{10})aryl(C_1 - C_6)alkyl or (C_2 - C_9)heteroaryl(C_1 - C_6)alkyl; and $R^{14}(C_1-C_6)alkyl$ wherein R^{14} is (C_1 - C_6)acylpiperazino, (C_6 - C_{10})aryl piperazino, (C_2 - C_9)heteroaryl piperazino, (C_1 - C_6)alkylpiperazino, (C_6 - C_{10})aryl(C_1 - C_6)alkylpiperazino, (C_2 - C_9)heteroaryl(C_1 - C_6)alkylpiperazino, morpholino, thiomorpholino, piperidino, pyrrolidino, piperidyl, (C_1 - C_6)alkylpiperidyl, (C_6 - C_{10})aryl piperidyl, (C_2 - C_9)heteroaryl piperidyl, (C_6 - C_{10})aryl(C_1 - C_6)alkylpiperidyl, (C_2 - C_9)heteroaryl(C_1 - C_6)alkylpiperidyl or (C_1 - C_6)acylpiperidyl;

35 or X^1 and X^2 may be taken together to form a (C_3-C_6) cycloalkyl, a benzo-fused (C_3-C_6) cycloalkyl ring or a group of the formula (J₇):



wherein the carbon atom bearing the asterisk is the carbon to which X^1 and X^2 are attached, s and t are each independently 1 or 2, and W is CF_2 , O, S, SO_2 or NR^{15} , wherein R^{15} is hydrogen, $(C_1-C_6)alkyl$, $(C_6-C_{10})acyl$, $(C_6-C_{10})aryl$, $(C_2-C_9)heteroaryl$, $(C_6-C_{10})aryl(C_1-C_6)alkyl$, $(C_2-C_9)heteroaryl(C_1-C_6)alkyl$, $(C_1-C_6)alkylsulfonyl$, $(C_6-C_{10})aryl$ sulfonyl or $(C_1-C_6)alkyl(C=O)\cdot$;

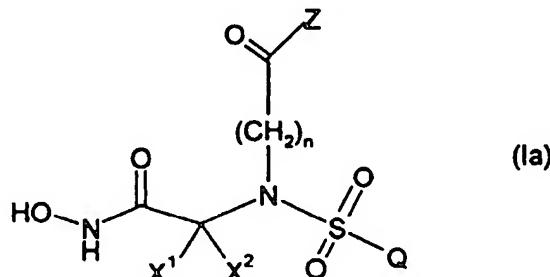
50 Q is (C₁-C₆)alkyl, (C₆-C₁₀)aryl, (C₆-C₁₀)aryloxy(C₆-C₁₀)aryl, (C₆-C₁₀)aryl(C₆-C₁₀)aryl, (C₆-C₁₀)aryl(C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₂-C₉)heteroaryl, (C₆-C₁₀)aryloxy(C₂-C₉)heteroaryl, (C₂-C₉)heteroaryl, (C₂-C₉)heteroaryl(C₂-C₉)heteroaryl, (C₂-C₉)heteroaryl(C₆-C₁₀)aryl, (C₁-C₆)alkyl(C₆-C₁₀)aryl, (C₁-C₆)alkoxy(C₆-C₁₀)aryl, ((C₁-C₆)alkoxy)₂(C₆-C₁₀)aryl, (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C₆-C₁₀)aryl, (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C₁-C₆)alkyl, (C₂-C₉)heteroaryloxy(C₆-C₁₀)aryl, (C₁-C₆)alkyl(C₂-C₉)heteroaryl, (C₁-C₆)alkoxy(C₂-C₉)heteroaryl, ((C₁-C₆)alkoxy)₂(C₂-C₉)heteroaryl, (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C₂-C₉)heteroaryl, (C₂-C₉)heteroaryloxy(C₂-C₉)heteroaryl, (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C₂-C₉)heteroaryl, (C₁-C₆)alkyl(C₂-C₉)heteroaryloxy(C₆-C₁₀)aryl, (C₁-C₆)alkyl(C₆-C₁₀)aryloxy(C₆-C₁₀)aryl, (C₁-C₆)alkyl(C₂-C₉)heteroaryloxy(C₆-C₁₀)aryl, (C₁-C₆)alkyl(C₆-C₁₀)aryloxy(C₆-C₁₀)aryl or (C₁-C₆)alkoxy(C₆-C₁₀)aryloxy(C₂-C₉)heteroaryl, wherein

each of the foregoing aryl groups may be optionally substituted by fluoro, chloro, bromo, trifluoromethyl, trifluoromethoxy, difluoromethoxy, (C₁-C₆)alkyl, (C₁-C₆)alkoxy or perfluoro(C₁-C₃)alkyl;
with the proviso that when either X¹ or X² is CH(R⁵)COR⁶ wherein R⁵ and R⁶ are as defined above, the other of X¹ or X² is hydrogen, (C₁-C₆)alkyl or benzyl.

5

[0017] One preferred embodiment of the present invention relates to a method of treating a disease, disorder or condition of the peripheral or central nervous system in a mammal, comprising the administration to a mammal a therapeutically effective amount of a compound of the formula (Ia):

10



or a pharmaceutically acceptable salt thereof, wherein X¹, X², Q and Z are as defined above, and n is an integer from 1 to 6.

25

[0018] Preferred methods of the invention comprise the administration of a compound of formula (Ia) wherein n is 2.

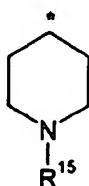
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Other preferred methods of the invention comprise the administration of a compound of formula (Ia) wherein Q is 4-methoxyphenyl or 4-phenoxyphenyl, optionally substituted by fluoro, chloro, bromo, trifluoromethyl, trifluoromethoxy, difluoromethoxy, (C₁-C₆)alkyl, (C₁-C₆)alkoxy or perfluoro(C₁-C₃)alkyl. Other preferred methods of the invention comprise the administration of a compound of formula (Ia) wherein either X¹ or X² is not hydrogen. Other preferred methods of the invention comprise the administration of a compound of formula (Ia) wherein Z is hydroxy, Q is 4-methoxyphenyl or 4-phenoxyphenyl, optionally substituted by fluoro, chloro, bromo, trifluoromethyl, trifluoromethoxy, difluoromethoxy, (C₁-C₆)alkyl, (C₁-C₆)alkoxy or perfluoro(C₁-C₃)alkyl, and either X¹ or X² is not hydrogen.

30

[0019] Other preferred methods of the invention comprise the administration of a compound of formula (Ia) wherein Q is 4-methoxyphenyl or 4-phenoxyphenyl and X¹ and X² are taken together to form (C₃-C₆)cycloalkyl, oxacyclohex-anyl, thiocyclohexanyl, indanyl or a group of the formula:

35



40

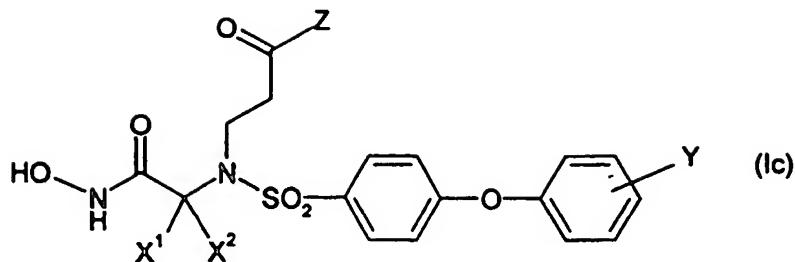
wherein the carbon bearing the asterisk is the carbon to which X¹ and X² are attached and R¹⁵ is (C₁-C₆)acyl, (C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₂-C₉)heteroaryl(C₁-C₆)alkyl or (C₁-C₆)alkylsulfonyl.

45

[0020] A more preferred embodiment of the present invention relates to a method of treating a disease, condition or disorder of the peripheral or central nervous system in a mammal comprising the administration of a therapeutically effective amount of a compound of the formula (Ic):

50

55



or the pharmaceutically acceptable salts thereof, wherein

15 X¹ is (C₁-C₆)alkyl;

X² is (C₁-C₆)alkyl; or

X¹ and X² taken together with the carbon atom to which they are attached form a ring selected from (C₅-C₇) cycloalkyl, 4-tetrahydropyranyl and 4-piperidinyl;

Z is hydroxy or (C₁-C₆)alkoxy; and

20 Y is a substituent on any of the carbon atoms of the phenyl ring capable of supporting an additional bond, preferably from 1 to 2 substituents (more preferably one substituent, most preferably one substituent in the 4-position) on the phenyl ring, independently selected from hydrogen, fluoro, chloro, trifluoromethyl, (C₁-C₆)alkoxy, trifluoromethoxy, difluoromethoxy and (C₁-C₆)alkyl.

[0021] The more preferred methods of the invention comprise the administration of a compound of formula (Ic) where-
25 in Y is hydrogen, fluoro or chloro, preferably 4-fluoro or 4-chloro. Other more preferred methods comprise the admin-
istration of a compound of formula (Ic) wherein X¹ and X² taken together with the carbon atom to which they are
attached form a cyclopentyl or 4-tetrahydropyranyl ring.

[0022] Other preferred methods of the invention comprise the administration of a compound of formula (Ic) wherein
30 X¹ and X² are both methyl. Other preferred methods comprise the administration of a compound of formula (Ic) wherein
Z is hydroxy.

[0023] Specifically, the most preferred methods of the invention comprise the administration of a compound of formula
(Ic) selected from the group consisting of:

35 3-[[4-(4-fluorophenoxy)benzenesulfonyl]- (1-hydroxycarbamoylcyclopentyl) amino]-propionic acid ethyl ester;

3-[[4-(4-fluorophenoxy)benzenesulfonyl]- (1-hydroxycarbamoylcyclopentyl) amino]propionic acid;

3-[[4-(4-fluorophenoxy)benzenesulfonyl]- (1-hydroxycarbamoyl-1-methylethyl) amino]propionic acid ethyl ester;

3-[[4-(4-fluorophenoxy)benzenesulfonyl]- (1-hydroxycarbamoyl-1-methylethyl) amino]propionic acid;

3-[[4-(4-fluorophenoxy)benzenesulfonyl]- (4-hydroxycarbamoyltetrahydropyran-4-yl)-amino]propionic acid;

40 3-[[4-(4-fluorophenoxy)benzenesulfonyl]- (4-hydroxycarbamoyltetrahydropyran-4-yl)-amino]propionic acid ethyl ester;

3-[[4-(4-chlorophenoxy)benzenesulfonyl]- (4-hydroxycarbamoyltetrahydropyran-4-yl)-amino]propionic acid;

3-[[4-(4-chlorophenoxy)benzenesulfonyl]- (4-hydroxycarbamoyltetrahydropyran-4-yl)-amino]propionic acid ethyl ester;

45 3-[(4-hydroxycarbamoyltetrahydropyran-4-yl)-(4-phenoxybenzenesulfonyl) amino]-propionic acid;

3-[(4-hydroxycarbamoyltetrahydropyran-4-yl)-(4-phenoxybenzenesulfonyl) amino]-propionic acid ethyl ester;

3-[[4-(4-fluorophenoxy)benzenesulfonyl]- (4-hydroxycarbamoylpiperidin-4-yl)amino]propionic acid ethyl ester;

3-[[4-(4-chlorophenoxy)benzenesulfonyl]- (1-hydroxycarbamoyl-1-methylethyl) amino]-propionic acid;

50 3-[[4-(4-chlorophenoxy)benzenesulfonyl]- (1-hydroxycarbamoyl-1-methylethyl) amino]-propionic acid ethyl ester;

3-[[4-(4-fluorophenoxy)benzenesulfonyl]- (1-hydroxycarbamoylcyclohexyl) amino]-propionic acid;

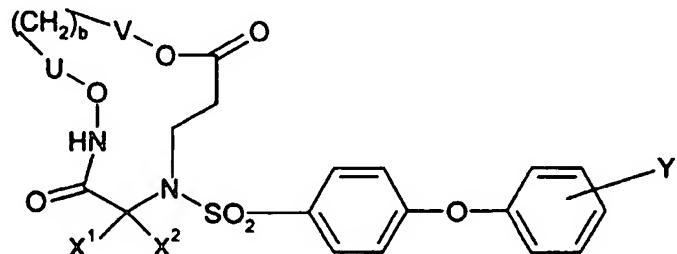
3-[(1-hydroxycarbamoylcyclopentyl)-(4-phenoxybenzenesulfonyl) amino]-propionic acid;

55 3-[[4-(4-chlorophenoxy)benzenesulfonyl]- (1-hydroxycarbamoylcyclopentyl) amino]-propionic acid

and pharmaceutically acceptable salts thereof.

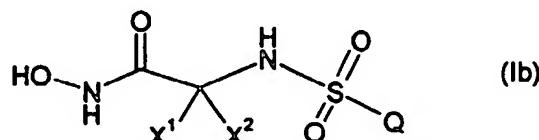
[0024] The methods of the invention also encompass methods of treating or preventing comprising administering a
55 prodrug of a compound of formula (I). A compound of formula (I) having a free amino, amido, hydroxy or carboxylic
acid group can be converted into a prodrug. Prodrugs include compounds wherein an amino acid residue, or a polypep-
tide chain of two or more (e.g., two, three or four) amino acid residues which are covalently joined through peptide
bonds to free amino, hydroxy or carboxylic acid groups of compounds of formula (I). The amino acid residues include

the 20 naturally occurring amino acids commonly designated by three letter symbols and also include, 4-hydroxyproline, hydroxylysine, demosine, isodemosine, 3-methylhistidine, norvalin, beta-alanine, gamma-aminobutyric acid, citrulline homocysteine, homoserine, ornithine and methionine sulfone. Prodrugs also include compounds wherein carbonates, carbamates, amides and alkyl esters which are covalently bonded to the above substituents of formula (I) through the carbonyl carbon prodrug sidechain. Prodrugs also include compounds of formula (I) in which the hydroxamic acid and carbonyl moiety when taken together, for example, form a group of the formula (Id):



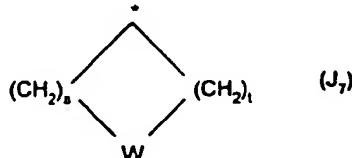
20 wherein X¹, X² and Y are as defined above and U and V are independently carbonyl, methylene, SO₂ or SO₃, and b is an integer from one to three wherein each methylene group is optionally substituted with hydroxy.

[0025] In addition to the foregoing preferred methods, further preferred embodiments of the present invention relates to a method of treatment of a condition, disease or disorder of the peripheral or central nervous system in a mammal comprising the administration of a compound of the formula (Ib):



wherein X¹, X² and Q are as defined above.

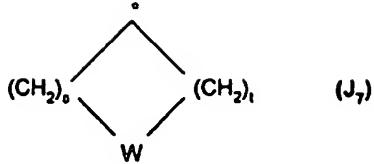
[0026] Other preferred methods comprise the administration of a compound of formula (Ib) wherein X¹ and X² are taken together to form a (C₃-C₆)cycloalkyl or benzo-fused (C₃-C₆)cycloalkyl ring or a group of formula J₇:



45 wherein the carbon atom bearing the asterisk is the carbon to which X¹ and X² are attached, s and t are independently 1 or 2; W is CF₂, S, O or NR¹⁶ and R¹⁶ is hydrogen, (C₁-C₆)alkyl, (C₆-C₁₀)aryl, (C₂-C₉)heteroaryl, (C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₂-C₉)heteroaryl(C₁-C₆)alkyl, (C₁-C₆)alkylsulfonyl, (C₆-C₁₀)arylalkylsulfonyl or acyl.

[0027] Other preferred methods comprise the administration of a compound of formula (Ib) wherein X¹ and X² are taken together to form a (C₃-C₆)cycloalkyl or benzo-fused (C₃-C₆)cycloalkyl ring. Other preferred methods comprise the administration of a compound of formula (Ib) wherein Q is (C₆-C₁₀)aryl, (C₆-C₁₀)aryl(C₆-C₁₀)aryl, (C₆-C₁₀)aryloxy(C₆-C₁₀)aryl, (C₆-C₁₀)aryloxy(C₂-C₉)heteroaryl, (C₂-C₉)heteroaryl, (C₂-C₉)heteroaryl(C₂-C₉)heteroaryl, (C₆-C₁₀)aryl(C₂-C₉)heteroaryl, (C₂-C₉)heteroaryl(C₆-C₁₀)aryl or (C₂-C₉)heteroaryloxy(C₆-C₁₀)aryl. Other preferred methods comprise the administration of a compound of formula (Ib) wherein X¹ and X² are each independently (C₁-C₆)alkyl.

[0028] Other more preferred methods comprise the administration of a compound of formula (Ib) wherein X¹ and X² are taken together to form a (C₃-C₆)cycloalkyl or benzo-fused (C₃-C₆)cycloalkyl ring or a group of the formula (J₇):



10 wherein the carbon atom bearing the asterisk is the carbon to which X¹ and X² are attached, s and t are independently 1 or 2 and Q⁹ is CF₂, S, O or NR¹⁶ wherein R¹⁶ is hydrogen, (C₁-C₆)alkyl, (C₆-C₁₀)aryl, (C₂-C₉)heteroaryl, (C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₂-C₉)heteroaryl(C₁-C₆)alkyl, (C₁-C₆)alkylsulfonyl, (C₆-C₁₀)arylsulfonyl or acyl; and Q is (C₆-C₁₀)aryl, (C₆-C₁₀)aryl(C₆-C₁₀)aryl, (C₆-C₁₀)aryloxy(C₆-C₁₀)aryl, (C₆-C₁₀)aryloxy-(C₂-C₉)heteroaryl, (C₂-C₉)heteroaryl, (C₂-C₉)heteroaryl(C₂-C₉)heteroaryl, (C₆-C₁₀)aryl(C₂-C₉)heteroaryl, (C₂-C₉)heteroaryl(C₆-C₁₀)aryl or (C₂-C₉)heteroaryloxy(C₆-C₁₀)aryl.

[0029] More preferred methods comprise the administration of a compound of formula (Ib) wherein X^1 and X^2 are taken together to form a (C_3 - C_6)cydoalkyl or benzo-fused (C_3 - C_6)cycloalkyl ring; and Q is (C_6 - C_{10})aryl, (C_6 - C_{10})aryl (C_6 - C_{10})aryl, (C_6 - C_{10})aryloxy(C_6 - C_{10})aryl, (C_6 - C_{10})aryloxy(C_2 - C_9)heteroaryl, (C_2 - C_9)heteroaryl, (C_2 - C_9)heteroaryl, (C_6 - C_{10})aryl(C_2 - C_9)heteroaryl, (C_2 - C_9)heteroaryl(C_6 - C_{10})aryl or (C_2 - C_9)heteroaryloxy(C_6 - C_{10})aryl.

[0030] More preferred methods comprise the administration of a compound of formula (Ib) wherein X^1 and X^2 are each independently (C_1 - C_6)alkyl; and Q is (C_6 - C_{10})aryl, (C_6 - C_{10})aryl(C_6 - C_{10})aryl, (C_6 - C_{10})aryloxy(C_6 - C_{10})aryl, (C_6 - C_{10})aryloxy(C_2 - C_9)heteroaryl, (C_2 - C_9)heteroaryl, (C_2 - C_9)heteroaryl(C_2 - C_9)heteroaryl, (C_6 - C_{10})aryl(C_2 - C_9)heteroaryl, (C_2 - C_9)heteroaryl(C_6 - C_{10})aryl or (C_2 - C_9)heteroaryloxy(C_6 - C_{10})aryl. More preferred methods utilize compounds of formula (Ib) wherein X^1 and X^2 are each independently (C_1 - C_6)alkyl; and Q is (C_6 - C_{10})aryloxy(C_6 - C_{10})aryl.

00311 Further, in addition to the methods stated above, other preferred methods comprise the administration of a

[305.] Further, in addition to the methods stated above, other preferred methods comprise the administration of a compound of formula (la), *supra*, wherein n is 1 and either of R¹ or R² is hydrogen. Other preferred methods comprise the administration of a compound of formula (la) wherein Z is alkoxy, Q is 4-methoxyphenyl or 4-phenoxyphenyl and either X¹ or X² is not hydrogen. More preferred methods comprise the administration of a compound of formula (la) wherein n is 2, Q is 4-methoxyphenyl or 4-phenoxyphenyl, R¹ and R² taken together to form piperazinyl, (C₁-C₆)alkylpiperazinyl, (C₆-C₁₀)aryl piperazinyl or (C₂-C₉)heteroaryl(C₁-C₆)alkylpiperazinyl, and either X¹ or X² is not hydrogen or both X¹ and X² are not hydrogen. More preferred methods comprise the administration of a compound of formula (la) wherein n is 2, Q is 4-methoxyphenyl or 4-phenoxyphenyl, R¹ is hydrogen or (C₁-C₆)alkyl, R² is 2-pyridylmethyl, 3-pyridylmethyl or 4-pyridylmethyl, and either X¹ or X² is not hydrogen or both X¹ and X² are not hydrogen. More preferred methods comprise the administration of a compound of formula (la) wherein n is 1, Q is 4-methoxyphenyl or 4-phenoxyphenyl, R¹ is hydrogen, R² is 2-pyridylmethyl, 3-pyridylmethyl or 4-pyridylmethyl, and either X¹ or X² is not hydrogen or both X¹ and X² are not hydrogen. More preferred methods comprise the administration of a compound of formula (la) wherein n is 2, Q is 4-methoxyphenyl, R¹ is hydrogen or (C₁-C₆)alkyl and R² is R³(C₂-C₆)alkyl wherein R³ is morpholino, thiomorpholino, piperidino, pyrrolidino, (C₁-C₆)acylpiperazino, (C₁-C₆)alkylpiperazino, (C₆-C₁₀)aryl-piperazino, (C₂-C₉)heteroaryl piperazino, (C₆-C₁₀)aryl(C₁-C₆)alkylpiperazino or (C₂-C₉)heteroaryl(C₁-C₆)alkylpiperazino and either X¹ or X² is not hydrogen or both X¹ and X² are not hydrogen. More preferred methods comprise the administration of a compound of formula (la) wherein n is 1, Q is 4-methoxyphenyl or 4-phenoxyphenyl, R¹ is hydrogen, R² is R³(C₂-C₆)alkyl wherein R³ is morpholino, thiomorpholino, piperidino, pyrrolidino, (C₁-C₆)acylpiperazino, (C₁-C₆)alkylpiperazino, (C₆-C₁₀)aryl piperazino, (C₂-C₉)heteroaryl piperazino, (C₆-C₁₀)aryl(C₁-C₆)alkylpiperazino or (C₂-C₉)heteroaryl(C₁-C₆)alkylpiperazino, and either X¹ or X² is not hydrogen or both X¹ and X² are not hydrogen.

[0032] In the foregoing discussion, the term "alkyl", as used herein, unless otherwise indicated, includes saturated monovalent hydrocarbon radicals having straight, branched or cyclic moieties or combinations thereof.

[0033] The term "alkoxy", as used herein, includes O-alkyl groups wherein "alkyl" is as defined above.

50 uents selected from the group consisting of fluoro, chloro, bromo, perfluoro(C₁-C₆)alkyl (including trifluoromethyl), (C₁-C₆)alkoxy, (C₆-C₁₀)aryloxy, perfluoro(C₁-C₃)alkoxy (including trifluoromethoxy and difluoromethoxy) and (C₁-C₆)alkyl. [0035] The term "heteroaryl", as used herein, unless otherwise indicated, includes an organic radical derived from

55 an aromatic heterocyclic compound by removal of one hydrogen, such as pyridyl, furyl, pyrrolyl, thienyl, isothiazolyl, imidazolyl, benzimidazolyl, tetrazolyl, pyrazinyl, pyrimidyl, quinolyl, isoquinolyl, benzofuryl, isobenzofuryl, benzothienyl, pyrazolyl, indolyl, isoindolyl, purinyl, carbazolyl, isoxazolyl, thiazolyl, oxazolyl, benzthiazolyl or benzoxazolyl, optionally substituted by 1 to 2 substituents selected from the group consisting of fluoro, chloro, trifluoromethyl, (C₁-C₆)alkoxy, (C₆-C₁₀)aryloxy, trifluoromethoxy, difluoromethoxy and (C₁-C₆)alkyl. Preferred heteroaryl groups include pyridyl, furyl, thienyl, isothiazolyl, pyrazinyl, pyrimidyl, pyrazolyl, isoxazolyl, thiazolyl or oxazolyl. Most preferred heteroaryl groups include pyridyl, furyl or thienyl.

[0036] The term "acyl", as used herein, unless otherwise indicated, includes a radical of the general formula RCO wherein R is alkyl, alkoxy, aryl, arylalkyl or arylalkyloxy and the terms "alkyl" or "aryl" are as defined above.

[0037] The term "acyloxy", as used herein, includes O-acyl groups wherein "acyl" is defined above.

5 [0038] The term "treating" refers to, and includes, reversing, alleviating, inhibiting the progress of, or preventing a disease, disorder or condition, or one or more symptoms thereof; and "treatment" and "therapeutically" refer to the act of treating, as defined above.

[0039] A "therapeutically effective amount" is any amount of any of the compounds utilized in the course of practicing the invention provided herein that is sufficient to reverse, alleviate, inhibit the progress of, or prevent a disease, disorder or condition, or one or more symptoms thereof.

10 [0040] The methods of the invention comprise the administration of a compound of formula (I) which may have chiral centers and therefore exist in different enantiomeric forms. This invention relates to all optical isomers, tautomers and stereoisomers of the compounds of formula (I) and mixtures thereof.

15 [0041] The present invention also relates to a method comprising the administration of a pharmaceutically acceptable acid addition salt of a compound of the formula (I). The possible acids which are used to prepare the pharmaceutically acceptable acid addition salts of the aforementioned base compounds of this invention are those which form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, such as the hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate, bisulfate, phosphate, add phosphate, acetate, lactate, citrate, acid citrate, tartrate, bitartrate, succinate, maleate, fumarate, gluconate, saccharate, benzoate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate and pamoate (i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)) salts.

20 [0042] The invention also relates to a method comprising the administration of a base addition salt of a compound of formula (I). The chemical bases that may be used as reagents to prepare pharmaceutically acceptable base salts of those compounds of formula (I) that are acidic in nature are those that form non-toxic base salts with such compounds. Such non-toxic base salts include, but are not limited to those derived from such pharmacologically acceptable cations such as alkali metal cations (e.g., potassium and sodium) and alkaline earth metal cations (e.g., calcium and magnesium), ammonium or water-soluble amine addition salts such as N-methylglucamine-(meglumine), and the lower alkanolammonium and other base salts of pharmaceutically acceptable organic amines.

25 [0043] The subject invention also relates to a method of treatment which relates to isotopically-labeled compounds, which are identical to those recited in formula (I), but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds relating to the present invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as 2H , 3H , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F , and ^{36}Cl , respectively. Compounds relating to the present invention, prodrugs thereof, and pharmaceutically acceptable salts of said compounds or of said prodrugs which contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this invention. Certain isotopically-labeled compounds of the present invention, for example those into which radioactive isotopes such as 3H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., 3H , and carbon-14, i.e., ^{14}C , isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium, i.e., 2H , can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced dosage requirements and, hence, may be preferred in some circumstances.

30 [0044] The present invention also relates to a pharmaceutical composition for the treatment of a disease, condition or disorder of the peripheral or central nervous system, wherein the disease, condition or disorder is Alzheimer's disease, stroke/cerebral ischemia, head trauma, spinal cord injury, multiple sclerosis, amyotrophic lateral sclerosis, Huntington's disease, Parkinson's disease, migraine, cerebral amyloid angiopathy, AIDS, age-related cognitive decline; mild cognitive impairment or a prion disease.

35 [0045] The present invention also relates to a pharmaceutical composition for treating of a disease, disorder or condition, wherein the disease, condition or disorder is arthritis (including osteoarthritis and rheumatoid arthritis), inflammatory bowel disease, Crohn's disease, emphysema, chronic obstructive pulmonary disease, Alzheimer's disease, organ transplant toxicity, cachexia, allergic reactions, allergic contact hypersensitivity, cancer, tissue ulceration, restenosis, periodontal disease, epidermolysis bullosa, osteoporosis, loosening of artificial joint implants, atherosclerosis (including atherosclerotic plaque rupture), aortic aneurysm (including abdominal aortic aneurysm and brain aortic aneurysm), congestive heart failure, myocardial infarction, stroke, cerebral ischemia, head trauma, spinal cord injury, neurodegenerative disorders (acute and chronic), inflammatory and autoimmune disorders, Huntington's disease, Parkinson's disease, migraine, depression, peripheral neuropathy, pain, cerebral amyloid angiopathy, nootropic or cognition enhancement, amyotrophic lateral sclerosis, multiple sclerosis, ocular angiogenesis, corneal injury, macular degeneration, abnormal wound healing, burns, diabetes, tumor invasion, tumor growth, tumor metastasis, corneal scarring, scleritis, AIDS, sepsis, septic shock, other diseases characterized by metalloproteinase activity or other diseases characterized by mammalian reprotoxin activity in a mammal, including a human, comprising an amount of a compound

of formula (I) or a pharmaceutically acceptable salt thereof effective in such treatments and a pharmaceutically acceptable carrier.

[0046] This invention also encompasses pharmaceutical compositions containing a prodrug of a compound of the formula (I). This invention also encompasses methods of treating or preventing disorders that can be treated or prevented by the inhibition of matrix metalloproteinases or the inhibition of mammalian reprodysin comprising a administering prodrug of compounds of the formula (I). A compound of formula (I) having a free amino, amido, hydroxy or carboxylic group can be converted into a prodrug. Prodrugs include compounds wherein an amino acid residue, or a polypeptide chain of two or more (e.g., two, three or four) amino acid residues which are covalently joined through peptide bonds to free amino, hydroxy or carboxylic acid groups of compounds of formula (I). The amino acid residues include the 20 naturally occurring amino acids commonly designated by three letter symbols and also include, 4-hydroxyproline, hydroxylysine, demosine, isodemosine, 3-methylhistidine, norvalin, beta-alanine, gamma-aminobutyric acid, citrulline, homocysteine, homoserine, ornithine and methionine sulfone. Prodrugs also include compounds wherein carbonates, carbamates, amides and alkyl esters which are covalently bonded to the above substituents of formula I through the carbonyl carbon prodrug side chain.

[0047] One of ordinary skill in the art will appreciate that the methods of the invention are useful in treating a diverse array of diseases. One of ordinary skill in the art will also appreciate that when using the methods of the invention in the treatment of a specific disease that the methods of the invention may be combined with various existing therapeutic methods and agents used for that disease.

[0048] The present invention also relates to combination therapies using, or combination pharmaceutical compositions comprising, a compound of formula (I) and, e.g., a standard non-steroidal anti-inflammatory drug (NSAID'S), such as piroxicam, diclofenac, a propionic acid, such as naproxen, flubiprofen, fenoprofen, ketoprofen and ibuprofen, a fenamate, such as mefenamic acid, indomethacin, sulindac, apazone, a pyrazolone, such as phenylbutazone; a salicylate, such as aspirin; an analgesic or intraarticular therapy, such as a corticosteroid and a hyaluronic acid, such as hyalgan and synvisc; an immune suppressant, such as cyclosporin, interferon, etc., e.g., in organ transplant therapy; a TNF- α inhibitor agent, such as an anti-TNF monoclonal antibody, a TNF receptor immunoglobulin molecule (such as Enbrel \circledR), low dose methotrexate, lefunimide, hydroxychloroquine, d-penicillamine, auranofin, parenteral gold, oral gold, etc.

[0049] The methods of present invention also relate to combination therapies using or combination pharmaceutical compositions comprising, a compound of formula (I) and, e.g., a CNS agent or agents, such as an antidepressant (e.g., sertraline, fluoxetine, paroxetine, etc.); an anti-Parkinsonian drug, such as deprenyl, L-dopa, requip, miratex, etc.; a MAOB inhibitor, such as selegiline, rasagiline, etc.; a COMP inhibitor, such as tolcapone (*i.e.*, Tasmar); an A-2 inhibitor; a dopamine reuptake inhibitor; an NMDA antagonist; a nicotine agonist; a dopamine agonist; an inhibitor of neuronal nitric oxide synthase; an anti-Alzheimer's drug; an acetylcholinesterase inhibitor, such as metrifonate, donepezil (*i.e.*, Aricept), Exelon (*i.e.*, ENA 713 or rivastigmine), etc.; tetrahydroaminoacridine (*i.e.*, Tacrine, Cognex, or THA); a COX-1 or COX-2 inhibitor, such as celecoxib (*i.e.*, Celebrex), rofecoxib (*i.e.*, Vioxx), etc.; propentofylline; an anti-stroke medication; an NR2B selective antagonist; a glycine site antagonist; a neutrophil inhibitory factor (NIF), etc. The methods of the present invention further relate to combination therapies using, or combination pharmaceutical compositions comprising, a compound of formula (I) and, e.g., an estrogen; a selective estrogen modulator, such as estrogen, raloxifene, tamoxifene, droloxifene, lasofoxifene, etc. The methods of the present invention also relate to combination therapies using, or combination pharmaceutical compositions comprising, a compound of formula (I) and, e.g., an agent that results in reduction of A β 1-40/1-42, such as an amyloid aggregation inhibitor, a secretase inhibitor, etc.

[0050] Further, the methods of present invention also relate to combination therapies using, or combination pharmaceutical compositions comprising, a compound of formula (I) and, e.g., an osteoporosis agents such as droloxifene or fosomax and immunosuppressant agents such as FK-506 and rapamycin. The methods of present invention also relate to combination therapies using, or combination pharmaceutical compositions comprising, a compound of formula (I) and, e.g., an anticancer agent, such as endostatin and angiostatin; a cytotoxic drug, such as adriamycin, daunomycin, cis-platinum, etoposide, taxol, taxotere or an alkaloid, such as vincristine; an antimetabolite, such as methotrexate; a cardiovascular agent, such as calcium channel blockers; a lipid lowering agent, such as a statin, a fibrate, a beta-blocker, an ACE inhibitor, an angiotensin-2 receptor antagonist or a platelet aggregation inhibitor. The methods of present invention also relate to combination therapies comprising the administration of compounds of formula (I) and another treatment, such as, e.g., fetal implant surgery treatment, gene therapy, etc.

DETAILED DESCRIPTION OF THE INVENTION

[0051] Matrix metalloproteinase inhibitors, including MMP-2 and MMP-9 selective inhibitors, utilized in accordance with the methods of the present invention, can be prepared according to methods well known to those of ordinary skill in the art. Specifically, methods for the preparation of the α -sulfonylamino hydroxamic acid matrix metalloproteinase inhibitors used in the methods of the present invention have been described in PCT Publication WO 96/27583, published

March 7, 1996, filed as U.S. Patent Application No. 08/401,049 on March 8, 1995; PCT Publication WO 98/33768, published August 6, 1998, filed as U.S. Patent Application No. 09/355,163 on January 12, 1998; and PCT Publication WO 99/07675, published February 18, 1999, filed as U.S. Patent Application No. 60/055,207 on August 8, 1997. The content of the foregoing U.S. patent applications are hereby incorporated in their entirety by reference. Isotopically labeled compounds of formula (I) of this invention and prodrugs thereof can generally be prepared by carrying out the procedures disclosed in the Schemes and/or in the Examples and Preparations of the foregoing incorporated applications, by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent.

5 [0052] The following additional U.S. patent applications relating specifically to other matrix metalloproteinase inhibitors with broad activity and their methods of preparation are also hereby incorporated by reference: U.S. Patent Application No. 09/154,969, filed September 17, 1998 which refers to non-selective cyclic aryl sulfonamino hydroxamic acids; U.S. Patent Application No. 08/855,023, filed May 13, 1997 which refers to cyclic imides as MMP inhibitors; U.S. Patent Application No. 08/881,092, filed July 9, 1997, which refers to cyclic sulfone hydroxamic acids useful as MMP inhibitors; U.S. Patent Application No. 09/242,504, filed July 25, 1997, which refers to aryl sulfonamino hydroxamic acids; U.S. Patent Application No. 08/892,417 filed July 14, 1997 which refers to phosphanates that are useful as MMP inhibitors; U.S. Patent Application No. 09/125,055, filed January 16, 1998, which refers to cyclic aryl sulfonamino hydroxamic acids useful in MMP inhibitors; U.S. Patent Application No. 09/341,226, filed January 27, 1998, which refers to N-hydroxy- β -sulfonyl propionamides useful as MMP inhibitors; U.S. Patent Application No. 09/331,275, filed December 18, 1997, which refers to cyclic sulfones as useful MMP inhibitors; U.S. Patent Application Ser. No. 09/233,883, filed January 20, 1999; U.S. Patent Application No. 09/216,402, filed December 18, 1998; U.S. Patent Application No. 09/130,922, filed August 6, 1998; (U.S. Patent Application No. 09/290022, filed April 9, 1999, U.S. Patent Application No. 09/287930, filed April 7, 1999; and U.S. Patent Application No. 09/287,508, filed April 7, 1999.

10 [0053] Further applications relating to matrix metalloproteinase inhibitor compounds hereby incorporated by reference are the following: PCT Application No. PCT/EP98/08565, filed December 23, 1998; and PCT Application No. PCT/EP98/06640, filed October 9, 1998.

15 [0054] The ability of matrix metalloproteinase inhibitors or their pharmaceutically acceptable salts (hereinafter also referred to as the inhibitors utilized in the present invention) to inhibit matrix metalloproteinases and a demonstration of their effectiveness for treating diseases of the peripheral and central nervous system is shown by the following *in vitro* assay tests.

20 [0055] In studying the regulation of genes in cytokine-stimulated human astrocytes, over-expression of one of the endogenous inhibitors of MMP, TIMP-1 (Tissue Inhibitor of Metalloproteinase 1) has been detected. In AD and age-matched controlled brains, increased expression of TIMP-1, MMP-2 and MMP-9 has been observed. Increased expression of two of the MMP's known to be inhibited by TIMP-1, MMP-2 and MMP-9, has been demonstrated (See, Table 1). Brain tissue from the hippocampus and superior frontal gyrus (SFG) have been selected for analysis because they are severely affected by AD degeneration; cerebellum was studied because it is relatively unaffected by the disease process. It has been determined that the expression of MMP-2, MMP-9 and TIMP-1 are all increased in the hippocampus and SFG. MMP-2 and -9 are also up-regulated in the cerebellum but perhaps not to as great an extent.

Table 1.

40

| Ratio of mRNA Expression in AD v. Age-matched Control Brain Regions. | | | |
|--|--------------------|---------------|-------------------|
| | Hippocampus Region | SFG Region | Cerebellum Region |
| MMP-2 | 2.5 (p=0.002) | 2.4 (p=0.006) | 1.5 (p=0.033) |
| MMP-9 | 3.3 (p=0.040) | 6.4 (p=0.006) | 2.5 (p=0.045) |
| TIMP-1 | 1.8 (p=0.006) | 2.2 (p=0.003) | 1.1 (p=0.541) |

45

Biological Assay

50 [0056] The following assays may be used to identify matrix metalloproteinase inhibitors.

Inhibition of Human Collagenase (MMP-1)

55 [0057] Human recombinant collagenase is activated with trypsin using the following ratio: 10 μ g trypsin per 100 μ g of collagenase. The trypsin and collagenase are incubated at room temperature for 10 minutes then a five fold excess (50 μ g/10 μ g trypsin) of soybean trypsin inhibitor is added.

[0058] 10 mM stock solutions of inhibitors are made up in dimethyl sulfoxide and then diluted using the following Scheme:

10 mM → 120 µM → 12 µM → 1.2 µM → 0.12 µM

5 [0059] Twenty-five microliters of each concentration is then added in triplicate to appropriate wells of a 96 well microfluor plate. The final concentration of inhibitor will be a 1:4 dilution after addition of enzyme and substrate. Positive controls (enzyme, no inhibitor) are set up in wells D1-D6 and blanks (no enzyme, no inhibitors) are set in wells D7-D12.

10 [0060] Collagenase is diluted to 240 ng/ml and 25 µl is then added to appropriate wells of the microfluor plate. Final concentration of collagenase in the assay is 60 ng/ml.

[0061] Substrate (DNP-Pro-Cha-Gly-Cys(Me)-His-Ala-Lys(NMA)-NH₂) is made as a 5 mM stock in dimethyl sulfoxide and then diluted to 20 µM in assay buffer. The assay is initiated by the addition of 50 µl substrate per well of the microfluor plate to give a final concentration of 10 µM.

15 [0062] Fluorescence readings (360 nm excitation, 460 nm emission) were taken at time 0 and then at 20 minute intervals. The assay is conducted at room temperature with a typical assay time of 3 hours.

[0063] Fluorescence vs time is then plotted for both the blank and collagenase containing samples (data from triplicate determinations is averaged). A time point that provides a good signal (the blank) and that is on a linear part of the curve (usually around 120 minutes) is chosen to determine IC₅₀ values. The zero time is used as a blank for each compound at each concentration and these values are subtracted from the 120 minute data. Data is plotted as inhibitor concentration vs % control (inhibitor fluorescence divided by fluorescence of collagenase alone × 100). IC₅₀'s are determined from the concentration of inhibitor that gives a signal that is 50% of the control.

20 [0064] If IC₅₀'s are reported to be <0.03 µM then the inhibitors are assayed at concentrations of 0.03 µM, 0.003 µM, 0.0003 µM and 0.00003 µM.

Inhibition of Gelatinase (MMP-2)

25 [0065] Inhibition of gelatinase activity is assayed using the MCA-Pro-Leu-Gly-Leu-Dpa-Ala-Arg-NH₂ substrate (10 µM) under the same conditions as inhibition of human collagenase (MMP-1).

[0066] 72kD gelatinase is activated with 1 mM APMA (p-aminophenyl mercuric acetate) for 16-18 hours at 4°C and is diluted to give a final concentration in the assay of 25 ng/ml. Inhibitors are diluted as for inhibition of human collagenase (MMP-1) to give final concentrations in the assay of 30 µM, 3 µM, 0.3 µM and 0.03 µM. Each concentration is done in triplicate.

30 [0067] Fluorescence readings (320 nm excitation, 390 emission) are taken at time zero and then at 15 minutes intervals for 3 hours.

[0068] IC₅₀'s are determined as per inhibition of human collagenase (MMP-1). If IC₅₀'s are reported to be less than 0.03 µM, then the inhibitors are assayed at final concentrations of 0.03 µM, 0.003 µM, 0.0003 µM and 0.00003 µM.

Inhibition of Stromelysin Activity (MMP-3)

35 [0069] Inhibition of stromelysin activity is assayed using Mca-Arg-Pro-Lys-Pro-Val-Glu-Nva-Trp-Arg-Lys(Dnp)-NH₂ (3 µM) under conditions similar as in inhibition of human collagenase (MMP-1).

40 [0070] Human stromelysin is activated for 20-24 hours at 37°C with 2 mM APMA (p-aminophenyl mercuric acetate) and is diluted to give a final concentration in the assay of 50 ng/ml. Inhibitors are diluted as for inhibition of human collagenase (MMP-1) to give final concentrations in the assay of 30 µM, 3 pM, 0.3 pM, and 0.03 µM. Each concentration is done in triplicate.

45 [0071] Fluorescence readings (320 nm excitation, 390 emission) are taken at time zero and then at 15 minute intervals for 3 hours.

[0072] IC₅₀'s are determined as per inhibition of human collagenase (MMP-1). If IC₅₀'s are reported to be less than 0.03 µM, then the inhibitors are assayed at final concentrations of 0.03 µM, 0.003 µM, 0.0003 µM, and 0.00003 µM.

Inhibition of Gelatinase (MMP-9)

50 [0073] Inhibition of gelatinase activity is assayed using the MCA-Pro-Leu-Gly-Leu-Dpa-Ala-Arg-NH₂ substrate (10 µM) under the same conditions as inhibition of human collagenase (MMP-1).

[0074] 92kD gelatinase is activated with 1.5 mM APMA (p-aminophenyl mercuric acetate) for 2 hours at 37°C and is diluted to give a final concentration in the assay of 25 ng/ml. Inhibitors are diluted as for inhibition of human collagenase (MMP-1) to give final concentrations in the assay of 30 µM, 3 µM, 0.3 µM and 0.03 µM. Each concentration is done in triplicate.

55 [0075] Fluorescence readings (320 nm excitation, 390 emission) are taken at time zero and then at 15 minutes intervals for 3 hours.

[0076] IC₅₀'s are determined as per inhibition of human collagenase (MMP-1). If IC₅₀'s are reported to be less than 0.03 μ M, then the inhibitors are assayed at final concentrations of 0.03 μ M, 0.003 μ M, 0.0003 μ M and 0.00003 μ M.

Inhibition of MMP-13

5 [0077] Human recombinant MMP-13 is activated with 2 mM APMA (p-aminophenyl mercuric acetate) for 1.5 hours, at 37°C and is diluted to 240 μ g/ml in assay buffer (50 mM Tris, pH 7.5, 200 mM sodium chloride, 5 mM calcium chloride, 20 μ M zinc chloride, 0.02% brij). Twenty-five microliters of diluted enzyme is added per well of a 96 well microfluor plate. The enzyme is then diluted in a 1:4 ratio in the assay by the addition of inhibitor and substrate to give

10 a final concentration in the assay of 60 μ g/ml.

[0078] 10 mM stock solutions of inhibitors are made up in dimethyl sulfoxide and then diluted in assay buffer as per the inhibitor dilution scheme for inhibition of human collagenase (MMP-1): Twenty-five microliters of each concentration is added in triplicate to the microfluor plate. The final concentrations in the assay are 30 μ M, 3 μ M, 0.3 μ M, and 0.03 μ M.

15 [0079] Substrate (Dnp-Pro-Cha-Gly-Cys(Me)-His-Ala-Lys(NMA)-NH₂) is prepared as for inhibition of human collagenase (MMP-1) and 50 μ l is added to each well to give a final assay concentration of 10 μ M. Fluorescence readings (360 nM excitation; 450 emission) are taken at time 0 and every 5 minutes for 1 hour.

[0080] Positive controls consist of enzyme and substrate with no inhibitor and blanks consist of substrate only.

20 [0081] IC₅₀'s are determined as per inhibition of human collagenase (MMP-1). If IC₅₀'s are reported to be less than 0.03 μ M, inhibitors are then assayed at final concentrations of 0.03 μ M, 0.003 μ M, 0.0003 μ M and 0.00003 μ M.

Collagen film MMP-13 Assay

25 [0082] Rat type I collagen is radiolabeled with ¹⁴C acetic anhydride (T.E. Cawston and A.J. Barrett, *Anal. Biochem.*, 99, 340-345 (1979)) and used to prepare 96 well plates containing radiolabeled collagen films (Barbara Johnson-Wint, *Anal. Biochem.*, 104, 175-181 (1980)). When a solution containing collagenase is added to the well, the enzyme cleaves the insoluble collagen which unwinds and is thus solubilized. Collagenase activity is directly proportional to the amount of collagen solubilized, determined by the proportion of radioactivity released into the supernatant as measured in a standard scintillation counter. Collagenase inhibitors are, therefore, compounds which reduce the radioactive counts released with respect to the controls with no inhibitor present. One specific embodiment of this assay is described in detail below.

30 [0083] For determining the selectivity of compounds for MMP-13 versus MMP-1 using collagen as a substrate, the following procedure is used. Recombinant human proMMP-13 or proMMP-1 is activated according to the procedures outlined above. The activated MMP-13 or MMP-1 is diluted to 0.6 μ g/ml with buffer (50 mM Tris pH 7.5, 150 mM NaCl, 10 mM CaCl₂, 1 μ M ZnCl₂, 0.05% Brij-35, 0.02% sodium azide).

35 [0084] Stock solutions of test compound (10mM) in dimethylsulfoxide are prepared. Dilutions of the test compounds in the Tris buffer, above, are made to 0.2, 2.0, 20, 200, 2000 and 20000 nM.

[0085] 100 μ l of appropriate drug dilution and 100 μ l of diluted enzyme are pipetted into wells of a 96 well plate containing collagen films labeled with ¹⁴C-collagen. The final enzyme concentration is 0.3 μ g/ml while the final drug concentration is 0.1, 1.0, 10, 100, 1000 nM. Each drug concentration and control is analyzed in triplicate. Triplicate

40 controls are also run for the conditions in which no enzyme is present and for enzyme in the absence of any compound.

[0086] The plates are incubated at 37°C for a time period such that around 30 - 50% of the available collagen is solubilized - determined by counting additional control wells at various time points. In most cases around 9 hours of incubation are required. When the assay has progressed sufficiently, the supernatant from each well is removed and counted in a scintillation counter. The background counts (determined by the counts in the wells with no enzyme) are subtracted from each sample and the % release calculated in relation to the wells with enzyme only and no inhibitor. The triplicate values for each point are averaged and the data graphed as percent release versus drug concentration. IC₅₀'s are determined from the point at which 50% inhibition of release of radiolabeled collagen is obtained.

45 [0087] To determine the identity of the active collagenases in cartilage conditioned medium, assays were carried out using collagen as a substrate, cartilage conditioned medium containing collagenase activity and inhibitors of varying selectivity. The cartilage conditioned medium was collected during the time at which collagen degradation was occurring and thus is representative of the collagenases responsible for the collagen breakdown. Assays were carried out as outlined above except that instead of using recombinant MMP-13 or recombinant MMP-1, cartilage conditioned medium was the enzyme source.

55 IL-1 Induced Cartilage Collagen Degradation From Bovine Nasal Cartilage

[0088] This assay uses bovine nasal cartilage explants which are commonly used to test the efficacy of various compounds to inhibit either IL-1 induced proteoglycan degradation or IL-1 induced collagen degradation. Bovine nasal

cartilage is a tissue that is very similar to articular cartilage, i.e. chondrocytes surrounded by a matrix that is primarily type II collagen and aggrecan. The tissue is used because it: (1) is very similar to articular cartilage, (2) is readily available, (3) is relatively homogeneous, and (4) degrades with predictable kinetics after IL-1 stimulation.

5 [0089] Two variations of this assay have been used to assay compounds. Both variations give similar data. The two variations are described below:

Variation 1

10 [0090] Three plugs of bovine nasal cartilage (approximately 2 mm diameter x 1.5 mm long) are placed into each well of a 24 well tissue culture plate. One ml of serumless medium is then added to each well. Compounds are prepared as 10 mM stock solutions in DMSO and then diluted appropriately in serumless medium to final concentrations, e.g., 50, 500 and 5000 nM. Each concentration is assayed in triplicate.

15 [0091] Human recombinant IL-1 α (5ng/mL) (IL-1) is added to triplicate control wells and to each well containing drug. Triplicate control wells are also set up in which neither drug nor IL-1 are added. The medium is removed and fresh medium containing IL-1 and the appropriate drug concentrations is added on days 6, 12, 18 and 24 or every 3 - 4 days if necessary. The media removed at each time point is stored at -20°C for later analysis. When the cartilage in the IL-1 alone wells has almost completely resorbed (about day 21), the experiment is terminated. The medium is removed and stored. Aliquots (100 μ l) from each well at each time point are pooled, digested with papain and then analyzed for hydroxyproline content. Background hydroxyproline (average of wells with no IL-1 and no drug) is subtracted from each data point and the average calculated for each triplicate. The data is then expressed as a percent of the IL-1 alone average value and plotted. The IC₅₀ is determined from this plot.

Variation 2

25 [0092] The experimental set-up is the same as outlined above in Variation 1, until day 12. On day 12, the conditioned medium from each well is removed and frozen. Then one ml of phosphate buffered saline (PBS) containing 0.5 μ g/ml trypsin is added to each well and incubation continued for a further 48 hours at 37°C. After 48 hours incubation in trypsin, the PBS solution is removed. Aliquots (50 μ l) of the PBS/trypsin solution and the previous two time points (days 6 and 12) are pooled, hydrolyzed and hydroxyproline content determined. Background hydroxyproline (average of wells with no IL-1 and no drug) is subtracted from each data point and the average calculated for each triplicate. The data is then expressed as a percent of the IL-1 alone average value and plotted. The IC₅₀ is determined from this plot. In this variation, the time course of the experiment is shortened considerably. The addition of trypsin for 48 hours after 12 days of IL-1 stimulation likely releases any type II collagen that has been damaged by collagenase activity but not yet released from the cartilage matrix. In the absence of IL-1 stimulation, trypsin treatment produces only low background levels of collagen degradation in the cartilage explants.

Inhibition of Human 92 kD Gelatinase (MMP-9)

40 [0093] Inhibition of 92 kD gelatinase (MMP-9) activity is assayed using the Mca-Pro-Leu-Gly-Leu-Dpa-Ala-Arg-NH₂ substrate (10 μ M) under similar conditions as described above for the inhibition of human collagenase (MMP-1).

[0094] Human recombinant 92 kD gelatinase (MMP-9, gelatinase B) is activated for 2 hours with 1mM p-aminophenyl-mercuric acetate (from a freshly prepared 100 mM stock in 0.2 N NaOH) at 37°C.

45 [0095] 10 mM dimethylsulfoxide stock solutions of inhibitors are diluted serially in assay buffer (50 mM TRIS, pH 7.5, 200 mM NaCl, 5 mM CaCl₂, 20 μ M ZnCl₂, 0.02% BRIJ-35 (vol./vol.)) using the following scheme:

10 mM \rightarrow 120 μ M \rightarrow 12 μ M \rightarrow 1.2 μ M \rightarrow 0.12 μ M

50 [0096] Further dilutions are made as necessary following this same scheme. A minimum of four inhibitor concentrations for each compound are performed in each assay. 25 μ L of each concentration is then added to triplicate wells of a black 96 well U-bottomed microfluor plate. As the final assay volume is 100 μ L, final concentrations of inhibitor are the result of a further 1:4 dilution (i.e. 30 μ M \rightarrow 3 μ M \rightarrow 0.3 μ M \rightarrow 0.03 μ M, etc.). A blank (no enzyme, no inhibitor) and a positive enzyme control (with enzyme, no inhibitor) are also prepared in triplicate.

55 [0097] Activated enzyme is diluted to 100 ng/mL in assay buffer, 25 μ L per well is added to appropriate wells of the microplate. Final enzyme concentration in the assay is 25 ng/mL (0.27 nM).

[0098] A five mM dimethylsulfoxide stock solution of substrate (Mca-Pro-Leu-Gly-Leu-Dpa-Ala-Arg-NH₂) is diluted in assay buffer to 20 μ M. The assay is initiated by addition of 50 μ L of diluted substrate yielding a final assay concentration of 10 μ M substrate. A zero time fluorescence reading (320 excitation; 390 emission) is immediately taken and

subsequent readings are taken every fifteen minutes at room temperature with a PerSeptive Biosystems CytoFluor Multi-Well Plate Reader with the gain at 90 units.

[0099] The average value of fluorescence of the enzyme and blank are plotted versus time. An early time point on the linear part of this curve is chosen for IC_{50} determinations. The zero time point for each compound at each dilution is subtracted from the latter time point and the data then expressed as percent of enzyme control (inhibitor fluorescence divided by fluorescence of positive enzyme control $\times 100$). Data is plotted as inhibitor concentration versus percent of enzyme control. IC_{50} 's are defined as the concentration of inhibitor that gives a signal that is 50% of the positive enzyme control.

10 Aggrecanase Assay

[0100] Primary porcine chondrocytes from articular joint cartilage are isolated by sequential trypsin and collagenase digestion followed by collagenase digestion overnight and are plated at 2×10^5 cells per well into 48 well plates with 5 μ Ci / ml 35 S (1000 Ci/mmol) sulphur in type I collagen coated plates. Cells are allowed to incorporate label into their 15 proteoglycan matrix (approximately 1 week) at 37°C, under an atmosphere of 5% CO₂.

[0101] The night before initiating the assay, chondrocyte monolayers are washed two times in DMEM/ 1% PSF/G and then allowed to incubate in fresh DMEM /1% FBS overnight.

[0102] The following morning chondrocytes are washed once in DMEM/1%PSF/G. The final wash is allowed to sit on the plates in the incubator while making dilutions.

20 [0103] Media and dilutions can be made as described in the Table below.

| | |
|----------------|---|
| Control Media | DMEM alone (control media) |
| IL-1 Media | DMEM + IL-1 (5 ng/ml) |
| Drug Dilutions | <p>Make all compounds stocks at 10 mM in DMSO.</p> <p>Make a 100 μM stock of each compound in DMEM in 96 well plate. Store in freezer overnight.</p> <p>The next day perform serial dilutions in DMEM with IL-1 to 5 μM, 500 nM, and 50 nM.</p> <p>Aspirate final wash from wells and add 50 μl of compound from above dilutions to 450 μl of IL-1 media in appropriate wells of the 48 well plates.</p> <p>Final compound concentrations equal 500 nM, 50 nM, and 5 nM. All samples completed in triplicate with Control and IL-1 alone samples on each plate.</p> |

[0104] Plates are labeled and only the interior 24 wells of the plate are used. On one of the plates, several columns are designated as IL-1 (no drug) and Control (no IL-1, no drug). These control columns are periodically counted to 35 monitor 35S-proteoglycan release. Control and IL-1 media are added to wells (450 μ l) followed by compound (50 μ l) so as to initiate the assay. Plates are incubated at 37°C, with a 5% CO₂ atmosphere.

[0105] At 40-50 % release (when CPM from IL-1 media is 4-5 times control media) as assessed by liquid scintillation counting (LSC) of media samples, the assay is terminated (9-12 hours). Media is removed from all wells and placed in scintillation tubes. Scintillate is added and radioactive counts are acquired (LSC). To solubilize cell layers, 500 μ l of 40 papain digestion buffer (0.2 M Tris, pH 7.0, 5 mM EDTA, 5 mM DTT, and 1 mg/ml papain) is added to each well. Plates with digestion solution are incubated at 60°C overnight. The cell layer is removed from the plates the next day and placed in scintillation tubes. Scintillate is then added, and samples counted (LSC).

[0106] The percent of released counts from the total present in each well is determined. Averages of the triplicates are made with control background subtracted from each well. The percent of compound inhibition is based on IL-1 45 samples as 0% inhibition (100% of total counts).

Inhibition of soluble TNF Production

[0107] The ability of the compounds or the pharmaceutically acceptable salts thereof to inhibit the cellular production/ 50 release of TNF and, consequently, demonstrate their effectiveness for treating diseases involving the dysregulated of TNF is shown by the following *in vitro* assay:

Method for the evaluation of recombinant TNFa Converting Enzyme Activity. Preparation of recombinant TACE:

[0108] A DNA fragment coding for the signal sequence, prodomain and catalytic domain of TACE (amino acids 1-473), 55 was amplified by polymerase chain reaction using a human lung cDNA library as a template. The amplified fragment was cloned into pFastBac vector. The DNA sequence of the insert was confirmed for both the strands. A bacmid

prepared using pFastBac in *E. coli* DH10Bac was transfected into SF9 insect cells. The virus particles were amplified to P1, P2, P3 stages. The P3 virus was infected into both SF9 and High Five insect cells and grown at 27°C for 48 hours. The medium was collected and used for assays and further purification.

5 Preparation of fluorescent quenched substrate:

[0109] A model peptidic TNF- α substrate (LY-LeucineAlanineGlutamineAlanine-ValineArginineSerineSerineLysine (CMTR)-Arginine (LY=Lucifer Yellow; CMTR=5-carboxytetramethyl Rhodamine)) was prepared and the concentration estimated by absorbance at 560 nm (E560, 60,000 M⁻¹CM⁻¹) according to the method of Geoghegan, KF, "Improved 10 method for converting an unmodified peptide to an energy-transfer substrate for a proteinase." *Bioconjugate Chem.* 7, 385-391 (1995). This peptide encompasses the cleavage site on pro-TNF which is cleaved in vivo by TACE.

Enzyme reaction.

15 [0110] The reaction, carried out in a 96 well plate (Dynatech), was comprised of 70 μ l of buffer solution (25 mM Hepes-HCl, pH 7.5, plus 20 μ M ZnCl₂), 10 μ l of 100 μ M fluorescent quenched substrate, 10 μ l of a DMSO (5%) solution of test compound, and an amount of r-TACE enzyme which will cause 50% cleavage in 60 minutes - in a total volume of 100 μ l. The specificity of the enzyme cleavage at the amide bond between alanine and valine was verified by HPLC and mass spectrometry. Initial rates of cleavage were monitored by measuring the rate of increase in fluorescence at 20 530 nm (excitation at 409 nm) over 30 minutes. The experiment was controlled as follows: 1) for background fluorescence of substrate; 2) for fluorescence of fully cleaved substrate; 3) for fluorescence quenching or augmentation from solutions containing test compound.

[0111] Data was analyzed as follows. The rates from the non-test compound containing "control" reactions were averaged to establish the 100% value. The rate of reaction in the presence of test compound was compared to that in 25 the absence of compound, and tabulated as "percent of non-test compound containing control. The results were plotted as "% of control" vs. the log of compound concentration and a half-maximal point or IC₅₀ value determined. The IC₅₀ for the above assay is a measure of the inhibition of the TNF- α proteolytic activity of TACE. Blockage of binding of TNF- α to TACE as used herein is as described in United States Patents 5,830,742, issued November 3, 1998.

30 Monocyte Assay

[0112] Human mononuclear cells were isolated from anti-coagulated human blood using a one-step Ficoll-hypaque separation technique. (2) The mononuclear cells were washed three times in Hanks balanced salt solution (HBSS) with divalent cations and resuspended to a density of 2 \times 10⁶ /ml in HBSS containing 1% BSA. Differential counts 35 determined using the Abbott Cell Dyn 3500 analyzer indicated that monocytes ranged from 17 to 24% of the total cells in these preparations.

[0113] 180m of the cell suspension was aliquoted into flat bottom 96 well plates (Costar). Additions of compounds and LPS (100 ng/ml final concentration) gave a final volume of 200 μ l. All conditions were performed in triplicate. After 40 a four hour incubation at 37°C in an humidified CO₂ incubator, plates were removed and centrifuged (10 minutes at approximately 250 \times g) and the supernatants removed and assayed for TNF- α using the R&D ELISA Kit.

[0114] A group of preferred compounds, more preferably compounds of the formula (I), that can be identified by the methods of the present invention include those inhibitors that possess potent activity against MMP-2 and MMP-9 (preferably an IC₅₀ of less than 500nM, more preferably 100nM, most preferably 50nM) preferably wherein said MMP-2 and MMP-9 inhibitory activity is selective activity for MMP-2 and MMP-9. The compounds of formula (I) possess surprisingly selective activity against MMP-2 and MMP-9. Specifically, compounds of formula (I) have IC₅₀'s of less than 500nM against either or both of MMP-2 and MMP-9.

[0115] For administration to mammals, including humans, in accordance with the methods of treatment of the present invention, for the treatment of a disorder, conditions or disease of the peripheral or central nervous system, a variety of conventional routes may be used including oral, parenteral (e.g., intravenous, intramuscular or subcutaneous), buccal, anal and topical. In general, the compounds of the invention (hereinafter also known as the active compounds) will be administered at dosages between about 0.1 and 25 mg/kg body weight of the subject to be treated per day, preferably from about 0.3 to 5 mg/kg. Preferably the active compound will be administered orally or parenterally. However, some variation in dosage will necessarily occur depending on the condition of the subject being treated. The person responsible for administration will, in any event, determine the appropriate dose for the individual subject.

[0116] The compounds of the present invention can be administered in a wide variety of different dosage forms, in general, the therapeutically effective compounds of this invention are present in such dosage forms at concentration levels ranging from about 5.0% to about 70% by weight.

[0117] For oral administration, tablets containing various excipients such as microcrystalline cellulose, sodium citrate,

calcium carbonate, dicalcium phosphate and glycine may be employed along with various disintegrants such as starch (and preferably corn, potato or tapioca starch), alginic acid and certain complex silicates, together with granulation binders like polyvinylpyrrolidone, sucrose, gelation and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often very useful for tabletting purposes. Solid compositions of a similar

5 type may also be employed as fillers in gelatin capsules; preferred materials in this connection also include lactose or milk sugar as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral administration, the active ingredient may be combined with various sweetening or flavoring agents, coloring matter or dyes, and, if so desired, emulsifying and/or suspending agents as well, together with such diluents as water, ethanol, propylene glycol, glycerin and various like combinations thereof. In the case of animals, they are advantageously contained in an animal feed or drinking water in a concentration of 5-5000 ppm, preferably 25 to 500 ppm.

10 [0118] For parenteral administration (intramuscular, intraperitoneal, subcutaneous and intravenous use) in accordance with the present invention, a sterile injectable solution of the active ingredient is usually prepared. Solutions of a therapeutic compound of the present invention in either sesame or peanut oil or in aqueous propylene glycol may be employed. The aqueous solutions should be suitably adjusted and buffered, preferably at a pH of greater than 8, if 15 necessary and the liquid diluent first rendered isotonic. These aqueous solutions are suitable intravenous injection purposes. The oily solutions are suitable for intraarticular, intramuscular and subcutaneous injection purposes. The preparation of all these solutions under sterile conditions is readily accomplished by standard pharmaceutical techniques well known to those skilled in the art. In the case of animals, compounds can be administered intramuscularly or subcutaneously at dosage levels of about 0.1 to 50 mg/kg/day, advantageously 0.2 to 10 mg/kg/day given in a single 20 dose or up to 3 divided doses.

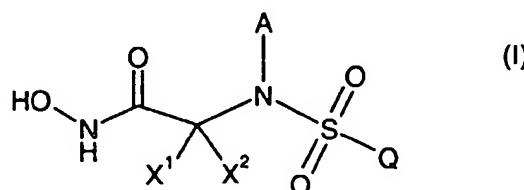
25 [0119] For the methods of the present invention, the active compounds herein disclosed may also be formulated in rectal compositions such as suppositories or retention enemas, e.g., containing conventional suppository bases such as cocoa butter or other glycerides.

30 [0120] For intranasal administration or administration by inhalation, the active compounds of the invention are conveniently delivered in the form of a solution or suspension from a pump spray container that is squeezed or pumped by the patient or as an aerosol spray presentation from a pressurized container or a nebulizer, with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. The pressurized container or nebulizer may contain a solution or suspension of the active compound. Capsules and cartridges (made, for example, from gelatin) for use in an inhaler or insufflator may be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

Claims

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1. The use of a compound of formula (I):



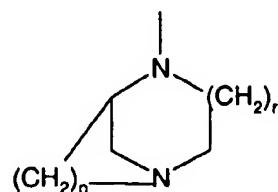
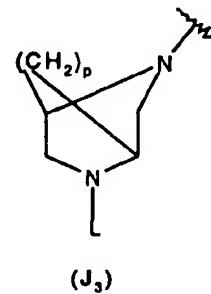
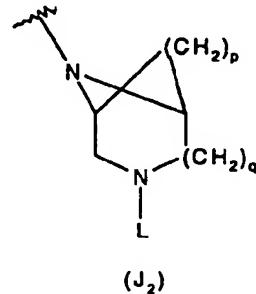
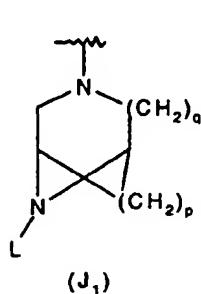
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or the pharmaceutically acceptable salts thereof, wherein

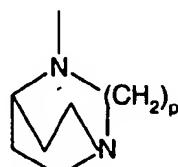
A is H or -(CH₂)_n-(C=O)-Z; where n is 1 to 6; and Z is hydroxy, (C₁-C₆)alkoxy or NR¹R² wherein R¹ and R² are each independently selected from the group consisting of hydrogen, (C₁-C₆)alkyl, piperidyl, (C₁-C₆)alkylpiperidyl, (C₆-C₁₀)arylpiperidyl, (C₂-C₉)heteroarylpirperidyl, (C₆-C₁₀)aryl(C₁-C₆)alkylpiperidyl, (C₂-C₉)heteroaryl(C₁-C₆)alkylpiperidyl, (C₁-C₆)acylpiperidyl, (C₆-C₁₀)aryl, (C₂-C₉)heteroaryl, (C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₂-C₉)heteroaryl(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₆-C₁₀)aryl, (C₆-C₁₀)aryl(C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, (C₃-C₆)cycloalkyl(C₁-C₆)alkyl, R⁵(C₂-C₆)alkyl, (C₁-C₅)alkyl(CHR³)(C₁-C₆)alkyl wherein R³ is hydroxy, (C₁-C₆)acyloxy, (C₁-C₆)alkoxy, piperazino, (C₁-C₆)acylamino, (C₁-C₆)alkylthio, (C₆-C₁₀)aryltliio, (C₁-C₆)alkylsulfinyl, (C₆-C₁₀)arylsulfinyl, (C₁-C₆)alkylsulfoxyl, (C₆-C₁₀)arylsulfoxyl, amino, (C₁-C₆)alkylamino, ((C₁-C₆)alkyl)₂ amino, (C₁-C₆)acylpiperazino, (C₁-C₆)alkylpiperazino, (C₆-C₁₀)aryl(C₁-C₆)alkylpiperazino, (C₂-C₉)heteroaryl(C₁-C₆)alkylpiperazino, morpholino, thiomorpholino, piperidino or pyrrolidino; R⁴(C₁-C₆)alkyl, (C₁-C₅)alkyl(CHR⁴)(C₁-C₆)alkyl wherein R⁴ is piperidyl, (C₁-C₆)alkylpiperidyl, (C₆-C₁₀)arylpiperidyl, (C₆-C₁₀)aryl(C₁-C₆)alkylpiperidyl, (C₂-C₉)heteroarylpirperidyl or (C₂-C₉)heteroaryl(C₁-C₆)alkylpiperidyl; and CH(R⁵)COR⁶ wherein R⁵ is hydrogen, (C₁-C₆)alkyl, (C₆-C₁₀)

5 aryl(C₁-C₆)alkyl, (C₂-C₉)heteroaryl(C₁-C₆)alkyl, (C₁-C₆)alkylthio(C₁-C₆)alkyl, (C₆-C₁₀)arylthio(C₁-C₆)alkyl, (C₁-C₆)alkylsulfinyl(C₁-C₆)alkyl, (C₆-C₁₀)arylsulfinyl(C₁-C₆)alkyl, (C₁-C₆)alkylsulfonyl(C₁-C₆)alkyl, (C₆-C₁₀)arylsulfonyl(C₁-C₆)alkyl, hydroxy(C₁-C₆)alkyl, amino(C₁-C₆)alkyl, (C₁-C₆)alkylamino(C₁-C₆)alkyl, ((C₁-C₆)alkylamino)₂(C₁-C₆)alkyl, R⁷R⁸NCO(C₁-C₆)alkyl or R⁷OCO(C₁-C₆)alkyl wherein R⁷ and R⁸ are each independently selected from the group consisting of hydrogen, (C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkyl and (C₂-C₉)heteroaryl(C₁-C₆)alkyl; and R⁶ is or R⁹R¹⁰N wherein R⁹ and R¹⁰ are each independently selected from the group consisting of hydrogen, (C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkyl and (C₂-C₉)heteroaryl(C₁-C₆)alkyl;

10 or R¹ and R², or R⁷ and R⁸, or R⁹ and R¹⁰ may be taken together to form an azetidinyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, indolinyl, isoindolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, (C₁-C₆)acylpiperazinyl, (C₁-C₆)alkylpiperazinyl, (C₆-C₁₀)arylpiperazinyl, (C₂-C₉)heteroarylpirperazinyl or a bridged diazabicycloalkyl ring selected from the group consisting of:



and



wherein

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p is 1, 2 or 3;

q is 1 or 2;

r is 0 or 1;

L is hydrogen, (C₁-C₆)alkyl or (C₁-C₆)acyl;

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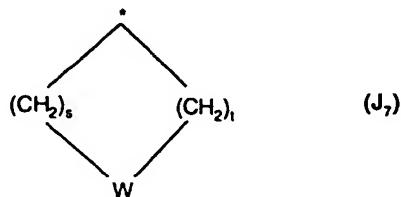
X¹ and X² are each independently selected from the group consisting of hydrogen, (C₁-C₆)alkyl, trifluoromethyl, trifluoromethyl(C₁-C₆)alkyl, (C₁-C₆)alkyl (difluoromethylene), (C₁-C₃)alkyl(difluoromethylene)(C₁-C₃)alkyl, (C₆-C₁₀)aryl, (C₂-C₉)heteroaryl, (C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₂-C₉)heteroaryl(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₆-C₁₀)aryl, (C₆-C₁₀)aryl(C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, (C₃-C₆)cycloalkyl(C₁-C₆)alkyl, hydroxy(C₁-C₆)alkyl, (C₁-C₆)acyloxy(C₁-C₆)alkyl, (C₁-C₆)alkoxy(C₁-C₆)alkyl, piperazinyl(C₁-C₆)alkyl, (C₁-C₆)acylamino(C₁-C₆)alkyl, piperidyl, (C₁-C₆)alkylpiperidyl, (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C₁-C₆)alkyl, (C₂-C₉)heteroaryl(C₁-C₆)alkoxy(C₁-C₆)alkyl, (C₁-C₆)alkoxy(C₁-C₆)alkyl, (C₁-C₆)alkylthio(C₁-C₆)alkyl, (C₆-C₁₀)arylsulfinyl(C₁-C₆)alkyl, (C₁-C₆)alkylsulfinyl(C₁-C₆)alkyl, (C₆-C₁₀)arylsulfonyl(C₁-C₆)alkyl, amino(C₁-C₆)alkyl, (C₁-C₆)alkylamino(C₁-C₆)alkyl, ((C₁-C₆)alkylamino)₂(C₁-C₆)alkyl, R¹¹CO(C₁-C₆)alkyl wherein R¹¹ is R¹²O or R¹²R¹³N wherein R¹² and R¹³ are each independently selected from the group consisting of hydrogen, (C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkyl or (C₂-C₉)heteroaryl(C₁-C₆)alkyl; and R¹⁴(C₁-C₆)alkyl wherein R¹⁴ is (C₁-C₆)acylpiperazino, (C₆-C₁₀)arylpiperazino, (C₂-C₉)heteroarylpirperazino, (C₁-C₆)alkylpiperazino, (C₆-C₁₀)aryl(C₁-C₆)alkylpiperazino, (C₂-C₉)heteroaryl(C₁-C₆)alkylpiperazino, morpholino, thiomorpholino, piperidino, pyrrolidino, piperidyl, (C₁-C₆)alkylpiperidyl, (C₆-C₁₀)arylpiperidyl, (C₂-C₉)heteroarylpirperidyl.

dyl, (C₆-C₁₀)aryl(C₁-C₆)alkylpiperidyl, (C₂-C₉)heteroaryl(C₁-C₆)alkylpiperidyl or (C₁-C₆)acylpiperidyl;

or X¹ and X² may be taken together to form a (C₃-C₆)cycloalkyl, a benzo-fused (C₃-C₆)cycloalkyl ring or a group of the formula (J₇):

5

10



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wherein the carbon atom bearing the asterisk is the carbon to which X¹ and X² are attached, s and t are independently 1 or 2, and W is CF₂, O, S, SO₂ or NR¹⁵, wherein R¹⁵ is hydrogen, (C₁-C₆)alkyl, (C₆-C₁₀)acyl, (C₆-C₁₀)aryl, (C₂-C₉)heteroaryl, (C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₂-C₉)heteroaryl(C₁-C₆)alkyl, (C₁-C₆)alkylsulfonyl, (C₆-C₁₀)arylsulfonyl or (C₁-C₆)alkyl(C=O);

20

Q is (C₁-C₆)alkyl, (C₆-C₁₀)aryl, (C₆-C₁₀)aryloxy(C₆-C₁₀)aryl, (C₆-C₁₀)aryl(C₆-C₁₀)aryl, (C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₂-C₉)heteroaryl, (C₆-C₁₀)aryloxy(C₂-C₉)heteroaryl, (C₂-C₉)heteroaryl, (C₂-C₉)heteroaryl(C₂-C₉)heteroaryl, (C₂-C₉)heteroaryl(C₆-C₁₀)aryl, (C₁-C₆)alkyl(C₆-C₁₀)aryl, (C₁-C₆)alkoxy(C₆-C₁₀)aryl, ((C₁-C₆)alkoxy)₂(C₆-C₁₀)aryl, (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C₆-C₁₀)aryl, (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C₁-C₆)alkyl, (C₂-C₉)heteroaryloxy(C₆-C₁₀)aryl, (C₁-C₆)alkyl(C₂-C₉)heteroaryl, (C₁-C₆)alkoxy(C₂-C₉)heteroaryl, ((C₁-C₆)alkoxy)₂(C₂-C₉)heteroaryl, (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C₂-C₉)heteroaryl, (C₂-C₉)heteroaryloxy(C₂-C₉)heteroaryl, (C₆-C₁₀)aryloxy(C₁-C₆)alkyl, (C₂-C₉)heteroaryloxy(C₁-C₆)alkyl, (C₁-C₆)alkyl(C₆-C₁₀)aryloxy(C₆-C₁₀)aryl, (C₁-C₆)alkyl(C₆-C₁₀)aryloxy(C₂-C₉)heteroaryl, (C₁-C₆)alkoxy(C₆-C₁₀)aryloxy(C₆-C₁₀)aryl, (C₁-C₆)alkoxy(C₂-C₉)heteroaryloxy(C₆-C₁₀)aryl or (C₁-C₆)alkoxy(C₆-C₁₀)aryloxy(C₂-C₉)heteroaryl, wherein each of the foregoing aryl groups may be optionally substituted by fluoro, chloro, bromo, trifluoromethyl, trifluoromethoxy, difluoromethoxy, (C₁-C₆)alkyl, (C₁-C₆)alkoxy or perfluoro(C₁-C₃)alkyl;

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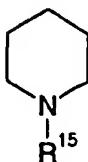
with the proviso that when either X¹ or X² is CH(R⁵)COR⁶ wherein R⁵ and R⁶ are as defined above, the other of X¹ or X² is hydrogen, (C₁-C₆)alkyl or benzyl;

30

in the manufacture of a medicament for the treatment in a mammal of a disease, condition or disorder of the peripheral or central nervous system, including but not limited to Alzheimer's disease, stroke/cerebral ischemia, head trauma, spinal cord injury, multiple sclerosis, amyotrophic lateral sclerosis, Huntington's disease, Parkinson's disease, migraine, cerebral amyloid angiopathy, AIDS, age-related cognitive decline, mild cognitive impairment and prion diseases.

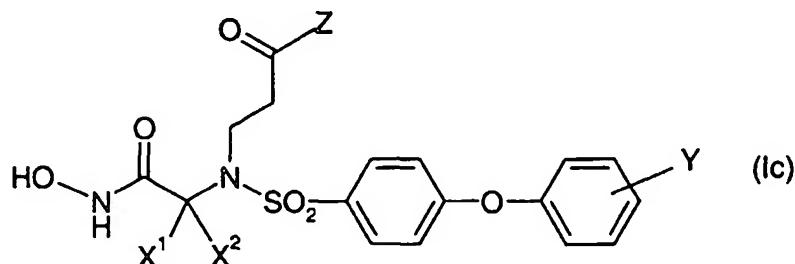
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2. Use according to Claim 1, wherein A is -(CH₂)_n-(C=O)-Z and Z and n are as defined in Claim 1.
3. Use according to Claim 2, wherein n is 2.
4. Use according to Claim 2, wherein Q is 4-methoxyphenyl or 4-phenoxyphenyl, optionally substituted by fluoro, chloro, bromo, trifluoromethyl, trifluoromethoxy, difluoromethoxy, (C₁-C₆)alkyl, (C₁-C₆)alkoxy or perfluoro(C₁-C₃)alkyl.
5. Use according to Claim 2, wherein Z is hydroxy, Q is 4-methoxyphenyl or 4-phenoxyphenyl, optionally substituted by fluoro, chloro, bromo, trifluoromethyl, trifluoromethoxy, difluoromethoxy, (C₁-C₆)alkyl, (C₁-C₆)alkoxy or perfluoro(C₁-C₃)alkyl, and either X¹ or X² is not hydrogen.
6. Use according to Claim 2, wherein Q is 4-methoxyphenyl or 4-phenoxyphenyl, optionally substituted by fluoro, chloro, bromo, trifluoromethyl, trifluoromethoxy, difluoromethoxy, (C₁-C₆)alkyl, (C₁-C₆)alkoxy or perfluoro(C₁-C₃)alkyl, and X¹ and X² are taken together to form (C₃-C₆)cycloalkyl, oxacyclohexanyl, thiacyclohexanyl, indanyl or a group of the formula



10 wherein R¹⁵ is (C₁-C₆)acyl, (C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₂-C₉)heteroaryl(C₁-C₆)alkyl or (C₁-C₆)alkylsulfonyl.

7. Use according to Claim 1, wherein the compound of formula (I) is a compound of formula (Ic):



25 or the pharmaceutically acceptable salts thereof, wherein

X¹ is (C₁-C₆)alkyl;
 X² is (C₁-C₆)alkyl; or
 30 X¹ and X² taken together with the carbon atom to which they are attached form a ring selected from (C₅-C₇) cycloalkyl 4-tetrahydropyranyl and 4-piperidinyl;
 Z is hydroxy or (C₁-C₆)alkoxy; and
 35 Y is a substituent on any of the carbon atoms of the phenyl ring capable of supporting an additional bond, preferably from 1 to 2 substituents (more preferably one substituent, most preferably one substituent in the 4-position) on the phenyl ring, independently selected from hydrogen, fluoro, chloro, trifluoromethyl, (C₁-C₆)alkoxy, trifluoromethoxy, difluoromethoxy and (C₁-C₆)alkyl.

8. Use according to Claim 7, wherein Y is fluoro or chloro.

9. Use according to Claim 7, wherein Y is fluoro or chloro at the 4-position of the phenoxy ring.

40 10. Use according to Claim 7, wherein X¹ and X² taken together with the carbon atom to which they are attached form a cyclopentyl or 4-tetrahydropyranyl ring.

11. Use according to Claim 7, wherein Z is hydroxy.

45 12. Use according to Claim 7, wherein the compound of formula (Ic) is selected from the group consisting of:

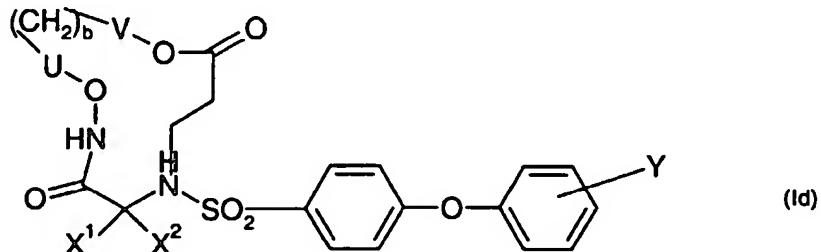
3-[[4-(4-fluorophenoxy)benzenesulfonyl]- (1-hydroxycarbamoylcyclopentyl)amino]propionic acid ethyl ester;
 3-[[4-(4-fluorophenoxy)benzenesulfonyl]- (1-hydroxycarbamoylcyclopentyl) amino]propionic acid;
 50 3-[[4-(4-fluorophenoxy)benzenesulfonyl]- (1-hydroxycarbamoyl-1-methylethyl) amino]propionic acid ethyl ester;
 3-[[4-(4-fluorophenoxy)benzenesulfonyl]- (1-hydroxycarbamoyl-1-methylethyl) amino]propionic acid;
 3-[[4-(4-fluorophenoxy)benzenesulfonyl]- (4-hydroxycarbamoyltetrahydropyran-4-yl)-amino]propionic acid;
 55 3-[[4-(4-fluorophenoxy)benzenesulfonyl]- (4-hydroxycarbamoyltetrahydropyran-4-yl)-amino]propionic acid ethyl ester;
 3-[[4-(4-chlorophenoxy)benzenesulfonyl]- (4-hydroxycarbamoyltetrahydropyran-4-yl)-amino]propionic acid;
 3-[[4-(4-chlorophenoxy)benzenesulfonyl]- (4-hydroxycarbamoyltetrahydropyran-4-yl)-amino]propionic acid ethyl ester;

3-[(4-hydroxycarbamoyltetrahydropyran-4-yl)-(4-phenoxybenzenesulfonyl)amino]-propionic acid;
 3-[(4-hydroxycarbamoyltetrahydropyran-4-yl)-(4-phenoxybenzenesulfonyl)amino]-propionic acid ethyl ester;
 3-[(4-(4-fluorophenoxy)benzenesulfonyl)-(4-hydroxycarbamoylpiperidin-4-yl)-amino]propionic acid ethyl ester;
 5 3-[(4-(4-chlorophenoxy)benzenesulfonyl)-(1-hydroxycarbamoyl-1-methylethyl)amino]-propionic acid;
 3-[(4-(4-chlorophenoxy)benzenesulfonyl)-(1-hydroxycarbamoyl-1-methylethyl)amino]-propionic acid ethyl ester;
 3-[(4-(4-fluorophenoxy)benzenesulfonyl)-(1-hydroxycarbamoylcyclohexyl)amino]-propionic acid;
 10 3-[(1-hydroxycarbamoylcyclopentyl)-(4-phenoxybenzenesulfonyl) amino]propionic acid;
 3-[(4-(4-chlorophenoxy)benzenesulfonyl)-(1-hydroxycarbamoylcyclopentyl)amino]-propionic acid

and pharmaceutically acceptable salts thereof.

13. The use of a prodrug compound of formula (Id):

15



wherein

30 X^1 is (C_1-C_6) alkyl;
 X^2 is (C_1-C_6) alkyl; or
 X^1 and X^2 taken together with the carbon atom to which they are attached form a ring selected from (C_5-C_7) cycloalkyl, 4-tetrahydropyranyl and 4-piperidinyl;

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Y is a substituent on any of the carbon atoms of the phenyl ring capable of supporting an additional bond, preferably from 1 to 2 substituents (more preferably one substituent, most preferably one substituent in the 4-position) on the phenyl ring, independently selected from hydrogen, fluoro, chloro, trifluoromethyl, (C_1-C_6) alkoxy, trifluoromethoxy, difluoromethoxy and (C_1-C_6) alkyl; and

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U and V are independently carbonyl, methylene, SO_2 or SO_3 , and b is an integer from one to three wherein each methylene group is optionally substituted with hydroxy; in the manufacture of a medicament for the treatment in a mammal of a disease, condition or disorder of the peripheral or central nervous system, including but not limited to Alzheimer's disease, stroke/cerebral ischemia, head trauma, spinal cord injury, multiple sclerosis, amyotrophic lateral sclerosis, Huntington's disease, Parkinson's disease, migraine, cerebral amyloid angiopathy, AIDS, age-related cognitive decline, mild cognitive impairment and prion diseases.

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14. A pharmaceutical composition useful in the treatment of a mammal afflicted with a disease, condition or disorder of the peripheral or central nervous system, including but not limited to Alzheimer's disease, stroke/cerebral ischemia, head trauma, spinal cord injury, multiple sclerosis, amyotrophic lateral sclerosis, Huntington's disease, Parkinson's disease, migraine, cerebral amyloid angiopathy, AIDS, age-related cognitive decline, mild cognitive impairment and prion diseases, which comprises a compound of formula (I) according to Claim 1 and a suitable carrier or excipient.

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15. The use of a compound of formula (I) according to Claim 1 in the manufacture of a medicament for the treatment in a mammal of a disease, condition or disorder of the peripheral or central nervous system, including but not limited to those described in Claim 1, for administration to a mammal concomitantly receiving a non-steroidal anti-inflammatory drug.

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16. The use of a compound of formula (I) according to Claim 1 in the manufacture of a medicament combined with a non-steroidal anti-inflammatory drug for the treatment in a mammal of a disease, condition or disorder of the peripheral or central nervous system, including but not limited to those described in Claim 1.

17. Use according to Claim 15 or 16 wherein the non-steroidal anti-inflammatory drug is selected from the group consisting of piroxicam, diclofenac, naproxen, flubiprofen, fenoprofen, ketoprofen and ibuprofen, fenamates, such as mefenamic acid, indomethacin, sulindac, apazone, and pyrazolones.

5 18. The use of a compound of formula (I) according to Claim 1 in the manufacture of a medicament for the treatment in a mammal of a disease, condition or disorder of the peripheral or central nervous system, including but not limited to those described in Claim 1, for administration to a mammal concomitantly receiving a COX-1 or COX-2 inhibitor.

10 19. The use of a compound of formula (I) according to Claim 1 in the manufacture of a medicament combined with a COX-1 or COX-2 inhibitor for the treatment in a mammal of a disease, condition or disorder of the peripheral or central nervous system, including but not limited to those described in Claim 1.

15 20. Use according to Claim 18 and 19 wherein the COX-2 inhibitor is selected from the group consisting of celecoxib and rofecoxib.

20 21. The use of a compound of formula (I) according to Claim 1 in the manufacture of a medicament for the treatment in a mammal of a disease, condition or disorder of the peripheral or central nervous system, including but not limited to those described in Claim 1, for administration to a mammal concomitantly receiving a CNS agent.

25 22. The use of a compound of formula (I) according to Claim 1 in the manufacture of a medicament combined with a CNS agent for the treatment in a mammal of a disease, condition or disorder of the peripheral or central nervous system, including but not limited to those described in Claim 1.

30 23. Use according to Claim 21 or 22 wherein the CNS agent is selected from the group consisting of an antidepressant selected from sertraline, fluoxetine, and paroxetine; an anti-Parkinsonian drug selected from deprenyl, L-dopa, and requip; miratex; MAOB inhibitors selected from selegiline, rasagiline; COMT inhibitors and tolcapone; A-2 inhibitors; dopamine reuptake inhibitors; NMDA antagonists; nicotine agonists; dopamine agonists; inhibitors of neuronal nitric oxide synthase; anti-Alzheimer's drugs; acetylcholinesterase inhibitors selected from galantamine, metrifonate, donepezil, Exelon, and tetrahydroaminoacridine; COX-1 inhibitors, COX-2 inhibitors selected from celecoxib and rofecoxib; propentofylline; an anti-stroke medication; NR2B selective antagonists; glycine site antagonists; and a neutrophil inhibitory factor (NIF).

35 24. The use of a compound of formula (I) according to Claim 1 in the manufacture of a medicament for the treatment in a mammal of a disease, condition or disorder of the peripheral or central nervous system, including but not limited to those described in Claim 1, for administration to a mammal concomitantly receiving an estrogen modulator.

40 25. The use of a compound of formula (I) according to Claim 1 in the manufacture of a medicament combined with an estrogen modulator for the treatment in a mammal of a disease, condition or disorder of the peripheral or central nervous system, including but not limited to those described in Claim 1.

45 26. Use according to claim 24 or 25 wherein the estrogen modulator is selected from the group consisting of estrogen, raloxifene, tamoxifene, droloxifene and lasofoxifene.

50 27. The use of a compound of formula (I) according to Claim 1 in the manufacture of a medicament for the treatment in a mammal of a disease, condition or disorder of the peripheral or central nervous system, including but not limited to those described in Claim 1, for administration to a mammal concomitantly receiving an agent that results in a reduction of A β 1-40/1-42.

28. The use of a compound of formula (I) according to Claim 1 in the manufacture of a medicament combined with an agent that results in a reduction of A β 1-40/1-42 for the treatment in a mammal of a disease, condition or disorder of the peripheral or central nervous system, including but not limited to those described in Claim 1.

55 29. Use according to Claim 28 and 29 wherein the agent that results in reduction of A β 1-40/1-42 is selected from the group consisting of amyloid aggregation inhibitors and secretase inhibitors.



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EP 00 30 8442

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